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NONINVASIVE METHODS IN CARDIOLOGY 2017

Edited by: **Cornélissen G., Siegelová J., Dobšák P.**

DEDICATED TO THE 85TH ANNIVERSARY OF PROFESSOR THOMAS KENNER

Brno 2017

Under the auspices of

Doc. PhDr. Mikuláš Bek, Ph.D., Rector of Masaryk University, Brno

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Prof. Dr. Thomas Kenner, D.h.c. mult. 85 years of age

Jarmila Siegelova

Dept. of Physiotherapy and Rehabilitation, Dept. of Sportsmedicine and Rehabilitation, Faculty of Medicine, Masaryk University, St. Anna´s Teaching Hospital, Brno

Figure 1: *Prof. Dr. Thomas Kenner, M.D., Dr. h.c. mult.*
Dr. h. c. Universität Jena, 1990
Dr. h. c., Semmelweis University Budapest, 1998
Dr. h. c., Masaryk University Brno, 2000
Head, Dept. of Physiology, Karl-Franzens-Universität Austria
Rektor (president) Karl-Franzens-Universität, Austria
Dean of Medical School, Karl-Franzens-Universität, Austria

Prof. Thomas Kenner is exceptional physiologist who focused primarily on physiology of cardiovascular system, covering diverse areas such as aerodynamic properties of arteries, chronobiology of cardiovascular system, pathophysiology and incidence of sudden infant death syndrome, physiology and monitoring of physiological functions in space.

Prof. Thomas Kenner was born in Vienna 29. 9. 1932. He studied medicine at University of Vienna, where he qualified in 1956. From 1956 to 1958 he worked in Dept. of Internal Medicine in Vienna. In 1959 he worked in Max Plank-Institut in Bad Nauheim in Germany. From 1959 to 1965 he was back to Vienna and worked in the Dept. of Experimental Pathology. Since 1963 he is married to Brigitte Hackl and has three children: Bernhard, born 1964, Lukas, born 1965 and Clara, born 1967. In 1965 he started work in Dept. of Physiology in Erlangen, Germany, where he began with University lectures in

Physiology, and in 1966 was appointed lecturer in Physiology (habilitation). He continued researching in cardiovascular physiology and from 1967 to 1968 he was a Visiting Scientist in Presbyterian Hospital in Philadelphia and Division of Biomedical Engineering, University of Virginia, and from 1969 to 1971 he worked as Associate Professor, Division of Biomedical Engineering, University of Virginia in Charlottesville, Virginia, USA. In 1971 Prof. Thomas Kenner was nominated for and got "Career Development Award" (NIH). In 1972 he was appointed full-time Professor and Chairman of the "Physiologisches Institut der Universität Graz". He worked as the head of the Dept. of Physiology until 2000, and in October 2000 he retired as Professor Emeritus of Karl-Franzens-Universität, Graz, Austria.

It is very difficult to describe the outstanding scientific, educational and organizational activities of Prof. Thomas Kenner in physiology. The Dept. of Physiology under his guidance flourished and attracted many researchers from different countries. His outstanding capabilities to carry out physiological experiments were were presented and published particularly in the area of cardiovascular physiology and cardiovascular pathology and in clinical disciplines, where his students continued in the experimental scientific work.

From 1989 to 1991 he was nominated Rektor (President) of Karl-Franzens-Universität and from 1991 to 1997 Dean of Medical School of Karl-Franzens-Universität, Graz, Austria. In this period a new building for theoretical Departments of Medical Faculty of Karl-Franzens-Universität was constructed in Graz under his administrative guidance.

His cooperation with other universities in Austria and abroad was renowned internationally, he collaborated with scientific groups from around the world, particularly in the USA and in European countries. Prof. Thomas Kenner won many honors and was member of scientific societies - Austrian Academy of Sciences, Academia Scientiarum et Artium Europaea, American Physiological Society, Cardiovascular Systems Dynamics Society, Deutsche Physiologische Gesellschaft, and Honorary Member of the Hungarian Physiological Society etc. He was nominated Professor honoris causa, University Ljubljana, Slovenia. In1993 he was honored from the Country Styria with "Großes Goldenes Ehrenzeichen des Landes Steiermark".

Prof. Thomas Kenner held many scientific positions, from 1978 to 1981 he was Member of the Life Science Working Group of the European Space Agency (ESA, Paris), from 1980 to 1987 he was Referee for Medicine in the "Kuratorium of the Austrian Research Fund (FWF)", from 1986 to 1988 he was President of "Cardiovascular System Dynamics Society", from 1985 to 1997 "Curriculum Dean of Medical School of University Graz, Austria". Prof. Thomas Kenner was nominated because of his exceptional scientific work and international cooperation Dr. honoris causa in Germany at "Universität Jena" (1990), in Hungary from Semmelweis University Budapest (1998), in the Czech Republic from Masaryk University Brno (2000).

Prof. Thomas Kenner cooperation with Faculty of Medicine, Masaryk University, Brno, Czech Republic started in 1991.Prof. Thomas Kenner was known in our University as a scientist from the publication about the dynamic of arterial pulses from the year 1968. We met personally for the first time in Prague in 1991 on International Physiological Congress, he was also accompanied by his wife Brigitte Kenner. Then he went to Masaryk University and at the meeting we signed an agreement of cooperation and since this time we were meeting every year once or twice in Brno, where we organized every year one Symposium about Chronobiology at Faculty of Medicine and one Symposium during Medical Trade Fair in Brno.

Usually we presented latest scientific discoveries together with Prof Thomas Kenner, Austria, Prof. Franz Halberg, Prof. Germaine Cornelissen, both USA, Prof. Jean-Paul Martineaud, Paris, France and

Brno team - Prof. Bohumil Fiser, Dr. Jiri Dusek and me. Sometimes Prof. Thomas Kenner, everytime accompanied by his wife, took also with him his pupils to Brno who presented at Masaryk University their scientific lectures. Prof. Thomas Kenner published some lectures in the scientific papers and they are included in selected publications. Brno chronobiological team visited also some scientific meetings in Graz and presented results in the area of cardiovascular control in man in health and diseases in Austria.

In 2012, Prof. Thomas Kenner continues his scientific activities, he actively participates in meetings across the world and publishes scientific papers. We are very glad and appreciate very much the long lasting cooperation with Prof. Thomas Kenner. Especially we esteem his friendship and collaboration, his enthusiasm and large scientific knowledge, which are all the time an inspiration for advancing the knowledge of cardiovascular physiology in health and pathology.

We have a great luck to cooperate with Prof. Thomas Kenner from nineties in the last century, he visited Brno every year two or three times, presented every time one or two lectures and dicussed with me, late Prof. Bohumil Fiser, CSc, Dr. Jiri Dusek,CSc, Prof. Petr Dobsak, CSc, late Prof. Jan Penaz, CSc, late Profesor Zdenek Placheta, DrSc., Prof. Pavel Braveny, CSc., Masaryk University and our other excelent scientist from abroad Prof. Dr. Franz Halberg, D.h.c, father of chronobiology, Prof. Dr. Germaine Cornelissen, University Minnesota, Halberg Chronobiology Center, USA, late Prof. Dr. Jean Paul Martineaud, Medical Faculty, University Paris, France, Prof. Jean Eric Wolf, University Dijon, France, Dr. Jean Christoph Eicher, University Dijon France and other cooperating visitors from Japan Prof. Masario Kohzuki University Sendai and Prof. Kohji Shirai, Toho University, Chiba. The presentations were published in Scripta Medica, Masaryk University Brno (included in SCOPUS database), in Abstracts books and in Noninvasive methods of Cardiology 1996, 1999, 2002, 2003, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016 and it is possible to find then on Masaryk University, CZ web sides and on web sides of University Minnesota USA. We wish him a many happy returns of his birthday and happiness with his wife Brigitte Kenner his family.

We have a privilege to have him in Masaryk University as a visiting professor and we wish him many happy returns at the occasion of his anniversary of eighty five years.

Ad multos Annos!

Figure 2: *Prof. MUDr. Jarmila Siegelová, DrSc, Dr. Othild Schwarzkoppf, Prof. Dr. Franz Halberg, Dr.h.c.mult., Prof. MUDr. Thomas Kenner,Dr.h.c.mult., Prof. MUDr. Bohumilf Fiser, CSc, Brno, Congress of Cardiology, 1997*

Figure 3: *Prof. Dr. Thomas Kenner, Dr.h.c.mult., Prof. MUDr. Jarmla Siegelova, DrSc., Congress of Noninvasive methods in Cardiology, Brno 2014*

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Figure 5: *Prof. Dr. Thomas Kenner, Dr.h.c.mult., Brigitte Kenner, Prof. MUDr. Jarmila Siegelova, DrSc., Congress of Noninvasive methods in Cardiology, Brno videopresntation with Prof. Dr. Germaine, Cornelissen, University of Minnesota, USA 2014*

Figure 6: *Prof. Thomas Kenner, Dr.h.c.mult., Brigitte Kenner, Graz University, Austria, Prof. MUDr. Jarmila Siegelová, DrSc., MUDr. Jiri Dusek, CSc., Congress of Cardiology, Brno, 2013*

Figure 7: *Prof. Dr. Thomas Kenner, Dr.h.c.mult. Austria and Prof. Dr. Kohji Shirai, Japan, Congress Noninvasive Methods in Cardiology, Brno 2012*

Figure 8: *Prof. Thomas Kenner, Dr.h.c.mult., Brigitte Kenner, Graz University, Austria, Prof. MUDr. Jarmila Siegelová, DrSc., Assoc. Prof. Dieter Platzer, Graz, Austria, MUDr. Jiri Dusek, CSc., Congress of Cardiology, Brno, 2015*

Figure 9: *Assoc. Prof. Dieter Platzer, Prof. Thomas Kenner, Dr.h.c.mult., Brigitte Kenner, Graz University, Austria, MUDr. Jiri Dusek, CSc., Prof. MUDr. Jarmila Siegelová, DrSc., Congress of Cardiology, Brno, 2015*

Figure 10: *Prof. Dr. Thomas Kenner, Dr.h.c.mult. Austria, Congress of Cardiology, Brno, 2015*

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Figure 12: *Anita Ertl, Prof.MUDr. Jarmila Siegelová, DrSc, Prof. Dr. Thomas Kenner, D.h.c.mult., Brigitte Kenner, Dept. of Physiology, University Graz, Austria 2016*

20 Years of History of Department of Sports Medicine and Rehabilitation

Prof. MUDr. Jarmila Siegelová, DrSc.
Department of Physiotherapy and Rehabilitation, Faculty of Medicine, Masaryk University, the Czech Republic

History

Two Departments - the Dept. of Functional Diagnostics and Sports Medicine of the Faculty of Medicine, Masaryk University and the Department of Rehabilitation of the St. Anna Teaching Hospital in Brno established the Department of Functional Diagnostics and Rehabilitation, Faculty of Medicine, Masaryk University, now the Dept. of Sports Medicine and Rehabilitation since 2010, headquartered in St. Anna Teaching Hospital in Brno in October 1, 1997. The history of both workplaces is different.

Department of Functional Diagnostics and Sport Medicine, Faculty of Medicine, St. Anna Teaching Hospital

In 1952, the Department of Sports Medicine was established, which was based in the Faculty Hospital and closely followed at the II. internal clinic of LF MU. The Clinic of Sport Medicine of St. Anna Teaching Hospital was established in 1983. The workplace was managed by Prof. MUDr. Jiří Polčák, DrSc., at that time already the head of II. Internal Clinics (1947 - 1971), from 1952 to 1963.

Department of Sports Medicine carried out teaching of students of medicine and also therapeutic and preventive activity under the vice-head of MUDr. Karel Kocnar (1953 - 1963).

Doc. MUDr. Vladimír Dražil, CSc. was the head of the Dept. of Sports Medicine from 1963 to 1983 and his vice-head for medical and preventive activities was MUDr. Karel Kocnar (1963-1983). Doc. MUDr. Vladimír Dražil, CSc. continued as the head of the Department until 1988. A part of the important staff of the clinic during this period was doc. MUDr. Jiří Rouš, CSc. (died 1985).

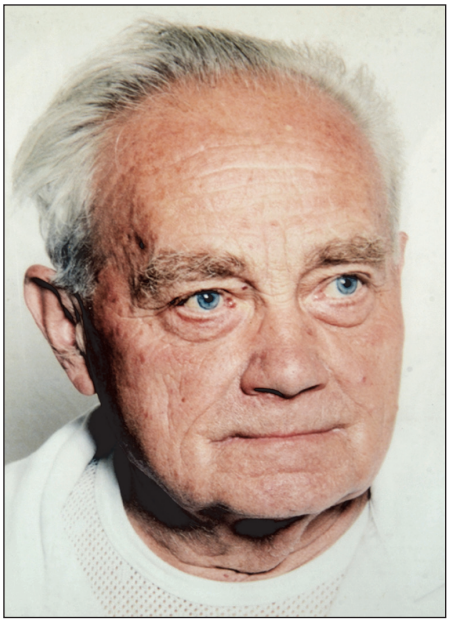

Figure 1: *Doc. MUDr. Vladimír Dražil, CSc., Head 1963 - 1988*

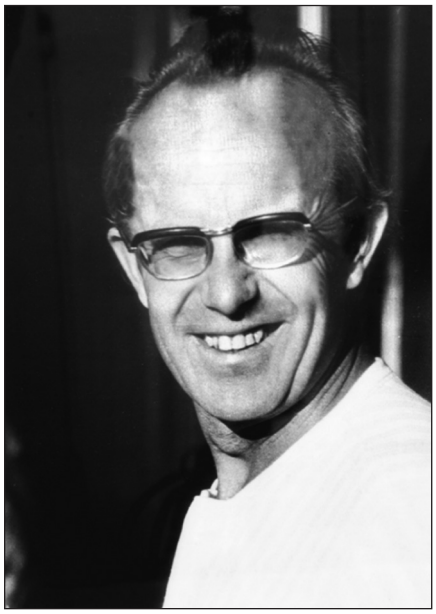

Figure 2: *Doc. MUDr. Jiří Rouš, CSc.*

In 1981, the Institute of Sports Medicine Prague was created from the Dept. Sports Medicine in Brno and the head was MUDr. Drahuška Blahová, anthropologist Marie Řezníčková, nurse Marie Sobková, who became a leading sister and later replaced by Olga Nezbedová.

In 1988 Prof. MUDr. Zdeněk Placheta, DrSc. became the head of the Department of Sports Medicine of and his vice-head for therapeutic and preventive activities was MUDr. Dušan Vítek (1983-1992). The department of Sports Medicine, Faculty of Medicine, Masaryk University, performed pedagogical activities - teaching of students of the Faculty of Medicine in the field of sports medicine, medical and preventive activities in the field of sports medicine and research activities, including the worldwide research program of the International Biological Program (IBM) in the 1970s.

Figure 3: *Prof. MUDr. Z. Placheta DrSc., Head 1988 - 1996*

Figure 4: *First row: Hrubá, M. Krainová, MUDr. J. Bušková, prof. MUDr. Z. Placheta, DrSc., MUDr. D. Blahová, MUDr. K. Kočnar, L. Třasoňová, A. Kotulánová, A. Pásková, second row prof. MUDr. J. Novotný, CSc., MUDr. I. Dohnalová, CSc., O. Korvasová, N. Tomanová, doc. MUDr. V. Dražil, MUDr. D. Vítek, RNDr. K. Čechovský, 1988*

Professor Placheta contributed to the renaming of the Dept. of Sports Medicine to the Dept. of Functional Diagnostics and Sports Medicine in 1991, in connection with organizational and economic changes in Czech health care. Thanks to the quality of results of his work and the modern concept of the content, based on the concept of Scandinavian clinical physiology and other experience from other European countries and the USA, the Dept. earned under the leadership of Prof. Z. Placheta the reputation of one of the best workplaces of its kind in the Czech Republic. The Department had 10 other doctors, the head nurse Věra Bednářová, later Ludmila Třasoňová and 10 nurses.

In 1996 Prof. MUDr. Jarmila Siegelová, DrSc. took over the management of Dept. of Functional Diagnostics and Sports Medicine.

Figure 5: *Prof. MUDr. Jarmila Siegelová, DrSc., Head of Dept. 1996 – 2007, Head of Dept. of Physiotherapy and Rehabilitation 2005 - 2012*

Prof. MUDr. Jarmila Siegelová, DrSc. has been cooperating since 1966 with the scientists from University of Tuebingen, Germany, with Professor Karel Brecht and Professor Hans Riecker and Prof. Dr. Nguyen-Duong Hoang, from 1970s with Professor Jean-Paul Martineud and Professor E. Savin at the Faculty of Medicine in Paris, France, from 1980s with Professor Franz Halberg and Professor Germaine Cornélissen of the University of Minnesota, USA, from 1990s with Professor Thomas Kenner of the University of Graz, Austria. All these collaborations she has transferred to the Department of Functional Diagnostics and Sports Medicine. Thus, two to three annual international scientific symposiums, conferences and workshops were organized by Prof. Siegelová.

In 2000 Rector of Masaryk University awarded the nomination of Doctor Honoris Causa to Professor Franz Halberg, University of Minnesota, USA, and Professor Thomas Kenner, University of Graz, Austria.

Figure 6: *Ing. H. Paperlein, Prof. MUDr. J. Siegelová, DrSc., Prof. Dr. Nguyen-Duong Hoang, Prof. Dr. H. Rieckert, I. Paperlein, University Tübingen, Germany*

Figure 7: *Professor Jean-Paul Martineaud, *27.3.1931-†29.11.2010, Faculty of Medicine, Paris, France*

Figure 8: *Professor Franz Halberg, M.D., Ph.D., Dr. h. c. multi, July 5, 1919 – June 9, 2013, University of Minnesota, USA*

Figure 9: *Prof. Dr. G. Cornélissen, University of Minnesota, USA, Director, Halberg´s Chronobiologic Center, University of Minnesota, USA (2002)*

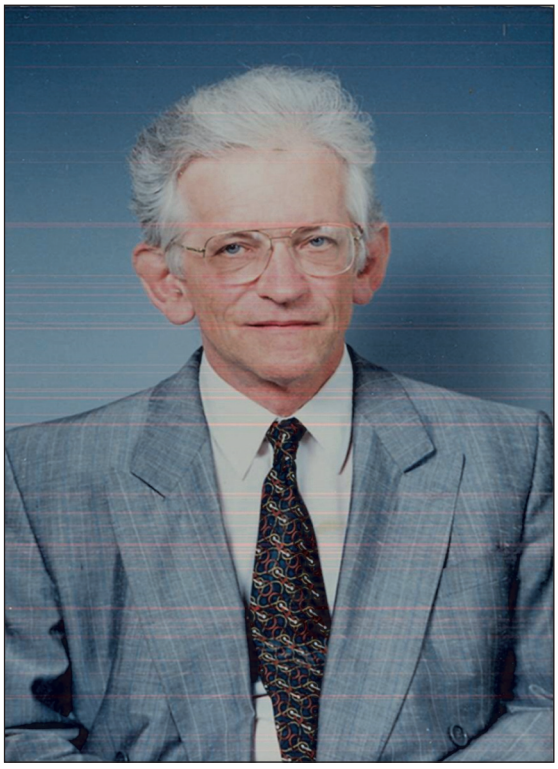

Figure 10: *Prof. Dr. Thomas Kenner, M.D., Dr. h.c. mult., Dean of Faculty of Medicine, Rector of University, University Graz, Austria*

Figure 11: *Awards of the title of Doctor Honoris Causa from Prof. RNDr. J. Zlatuška, CSc., Rector of Masaryk University to Professor F. Halberg, USA and Professor T. Kenner, Austria (Brno 2000)*

Figure 12: *Professor Franz Halberg, Professor Thomas Kenner, Prof. MUDr. Jarmila Siegelová, DrSc. (2000)*

Since 1997 Prof. MUDr. Petr Dobšák, CSc. has been working at the Department of Functional Diagnostics and Rehabilitation and he continued his earlier co-operation with Professor Jean-Eric Wolf and dr. Jean-Christoph Eischer and co-operation with Japanese scientists. In the Department of Functional Diagnostics and Rehabilitation there were given lectures from Prof. Kou Imachi, Dipl. Eng., PhD, University of Tokyo, Prof. Masaki Anraku, MD, PhD, University of Tokyo, Prof. Yusuke Abe, MD, PhD, University of Tokyo, Prof. Atsushi Baba, MD, PhD, University of Tokyo, Associate Prof. Itsuro Saito, Dipl.Eng., PhD, University of Tokyo, Associate Prof. Takashi Isoyama, Dipl. Eng., PhD, University of Tokyo, Prof. Kozaburo Hayashi, Dipl. Eng., PhD, University of Osaka, Prof. Shin-Ichi Nitta, MD, PhD, Tohoku University Sendai, Prof. Makoto Tamai, MD, PhD, Tohoku University Sendai, Prof. Masahiro Kohzuki, MD, PhD, Tohoku University Sendai, Associate Prof. Yusuke Inoue, Dipl. Eng., PhD, Tohoku University Sendai, Prof. Kouji Shirai, MD, PhD, Toho University Chiba, Dr. Kazuhiro Shimizu, MD, PhD, Toho University Chiba, Msc. Akihiro Ogawa, PhD, Toho University Chiba, Japan, and this continued in the Department too.

The Department of Functional Diagnostics and Rehabilitation continued to perform pedagogical activities - teaching students of the Faculty of Medicine in the field of internal medicine, since 1995 in bachelor‘s study of Physiotherapy, medical and preventive activities in the field of internal medicine, diagnostics of cardiovascular, respiratory and metabolic diseases and sports medicine.

Figure 13: *Prof. J.E. Wolf, Dijon, France (2008)*

Figure 14: *Prof. Dr. Masario Kohzuki, Sendai, Japan*

The Department of Sports Education and Rehabilitation organized international symposia, workshops and congresses every year, 2-3 times a year, attended by foreign colleagues from medical faculties and universities. These activities have led to a number of joint scientific publications and monographs.

Figure 15: *From the right MUDr. P. Homolka, Ph.D., MUDr. P. Vank, Prof. MUDr. B. Fišer, CSc., L. Tařsoňová, Prof. Dr. F. Halberg, MUDr. V. Zatloukal, CSc., Dr. O. Schwartzkopff, MUDr. J. Dušek, CSc., Prof. MUDr. J. Siegelová, DrSc., Prof. Dr. V. Chromý, DrSc., Prof. MUDr. J. Novotný, CSc. (1996)*

Figure 16: *MUDr. K. Kočnar, Prof. MUDr. Z. Placheta, DrSc. (1997)*

Figure 17: *Doc. MUDr. V. Dražil, CSc., Prof. MUDr. Z. Placheta, DrSc. (1997)*

Figure 18: *Prof. MUDr. Z. Placheta, DrSc., Doc. MUDr. J. Máčková, CSc., Prof. MUDr. J. Siegelová, DrSc., Prof. MUDr. J. Vítovec, CSc. (1997)*

Figure 19: *Doc. MUDr. T. Kára, Ph.D., Prof. MUDr. P. Dobšák, CSc., Prof. MUDr. M. Kučera, DrSc. (1997)*

Figure 20: *Prof. MUDr. J. Siegelová, DrSc., Prof. Dr. F. Halberg, d.h.c. multi, MUDr. J. Dušek, CSc. (2002)*

Figure 21: *Prof. Dr. G. Cornélissen, Prof. MUDr. J. Siegelová, DrSc. (2002)*

Figure 22: *From the right Prof. Dr. G. Cornélissen, Dr. O. Schwartzkopff, Prof. F. Halberg, Prof. H. Illnerová, DrSc., President of AV ČR, Prof. MUDr. J. Siegelová, DrSc. (2002)*

Figure 23: *From the right Prof. MUDr. J. Siegelová, DrSc., Prof. Dr. F. Halberg, Prof. MUDr. B. Fišer, CSc., MUDr. P. Homolka, Ph.D., Prof. Dr. G. Cornélissen, sitting Dr. O. Schwartzkopff, Prof. Dr. M. Havelková, DrSc. (2003)*

Figure 24: *From the left Prof. MUDr. B. Fišer, CSc., Prof. Dr. T. Kenner, B. Kenner, Doc. MUDr. M. Pohanka, Ph.D., Dr. O. Schwartzkopff, Prof. Dr. F. Halberg, MUDr. J. Dušek, CSc., Prof. MUDr. J. Siegelová, DrSc. (2008)*

Department of Rehabilitation

Medical rehabilitation at St. Anna Teaching Hospital was performed since the 1950s, first on orthopedics, later on in neurology, internal medicine and in other disciplines. Separate Rehabilitation Department was established in 1965 and the head of the Rehabilitation Department was at first MUDr. Silvio Koenig (born in 1923, died 1993) from 1965 to 1985. The department had 3 more physicians and 20 physiotherapists.

Prim. MUDr. Jitka Svobodová was the head of the Department from 1985 to 1997. The Department of Rehabilitation managed all physiotherapists (41) who had previously joined the clinics and provided rehabilitation care in all clinical disciplines. The first head of the physiotherapist staff was Helena Juráková, whose function was later taken over by Marie Falberová.

The important change of the Rehabilitation Department occurred in November 1992, when a bed unit was created. Bed unit No 23 had at the beginning 20 beds, later this number increased to 32 beds, which until now served to complete the early rehabilitation of clinical disciplines, mainly neurosurgery, orthopedics, neurology, surgery. Jarmila Georgová worked as a station nurse with the staff of 14 other nurses and 4 physiotherapists.

Physiotherapy is an integral part of the therapy of all clinical disciplines in St. Anna Teaching Hospital.

Figure 25: *Prim. MUDr. Jitka Svobodová, Head, Dept. of Rehabilitation 1985 – 1997, 1997 – 2009 Vicehead of the Department*

Department of Functional Diagnostics and Rehabilitation LF MU, St. Anna Teaching Hospital

On 1.10.1997 the Dept. of Functional Diagnostics and Rehabilitation was established from the Dept. of Functional Diagnostics and Sports Medicine and from the Department of Rehabilitation. The reasons for the establishment of the Dept. were the teaching of a bachelor‘s study of physiotherapy, which had a new possibility of pedagogical activity within the Faculty of Medicine of Masaryk University.

The Dean of Faculty of Medicine MU Prof. MUDr. Jiří Vorlíček, CSc. and the director of St. Anna Teaching Hospital in Brno, MUDr. Alena Štětková, CSc. supported the establishment of the Dept. of Functional Diagnostics and Rehabilitation.

Head of the Department of Functional Diagnostics and Rehabilitation was Prof. MUDr. Jarmila Siegelová, DrSc., her vice-heads for therapeutic preventive activity were MUDr. Jitka Svobodová and MUDr. Pavel Homolka, Ph.D. (until 2002), the head nurse was Ludmila Třasoňová (until 2002) and head physiotherapist Marie Falberová (until 2009), station nurse Eva Vránová.

Figure 26: *From the left MUDr. L. Bednařík, Prof. MUDr. J. Siegelová, DrSc., MUDr. A. Štětková, CSc., Director of St. Anna Teaching Hospital, Prof. MUDr. J. Vorlíček, CSc., Dean of Faculty of Medicine MU, Prof. MUDr. Z. Placheta, DrSc. (1.10.1997)*

Figure 27: *From the left MUDr. J. Svobodová, Prof. MUDr. J. Siegelová, DrSc., MUDr. A. Štětková, CSc., Director of St. Anna Teaching Hospital, Prof. MUDr. J. Vorlíček, CSc., Dean of Faculty of Medicine MU, Prof. MUDr. Z. Placheta, DrSc., Prof. MUDr. J. Novotný, CSc., MUDr. P. Homolka, Ph.D. (1.10.1997)*

Figure 28: *From the left MUDr. L. Bednařík, Prof. MUDr. J. Siegelová, DrSc., MUDr. A. Štětková, CSc., Director of St. Anna Teaching Hospital, Prof. MUDr. J. Vorlíček, CSc., Dean of Faculty of Medicine MU(1. 10. 1997)*

Figure 29: *Staff of the Department 1. 10. 1997*

Figure 30: *1.10.1997 the staff of the Department of Functional Diagnostics and Rehabilitation*

Figure 31: *1.10.1997 the staff of the Department of Functional Diagnostics and Rehabilitation*

Figure 32: *1.10.1997 the staff of the Department of Functional Diagnostics and Rehabilitation*

Figure 33: *From the left L. Třasoňová, Prof. MUDr. Z. Placheta, DrSc., Prof. Dr. J.P. Martineaud, Paris, France, B. Kenner, Prof. Dr. T. Kenner, Graz, Austria, vice-head MUDr. J. Svobodová (1997)*

Figure 34: *From the left Prof. MUDr. J. Siegelová, DrSc., B. Kenner, Prof. Dr. T. Kenner, Graz, Austria (1997)*

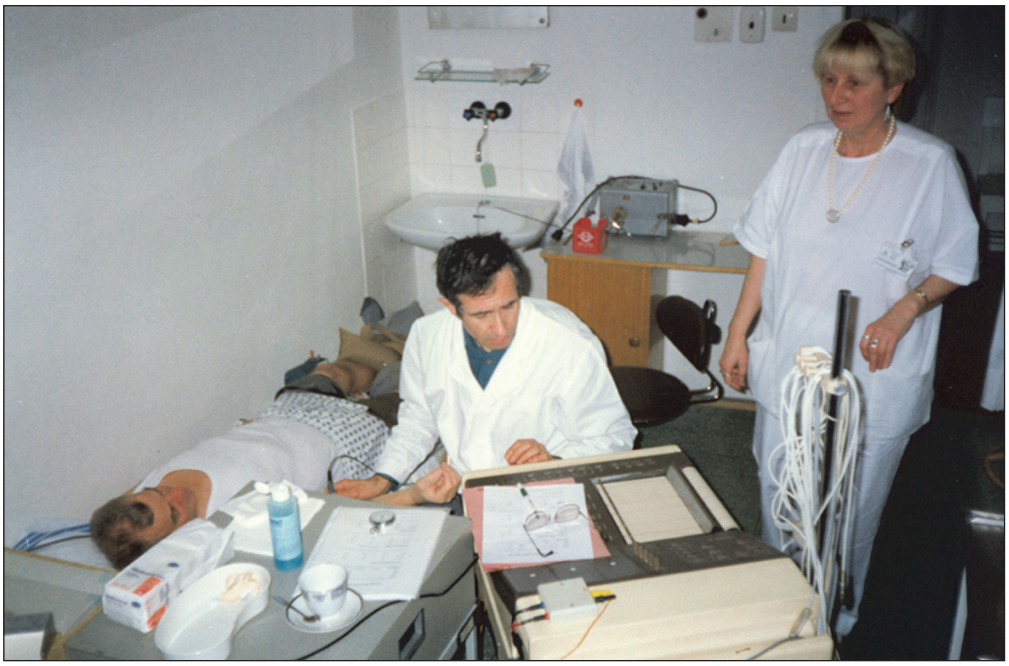

Figure 35: *Prof. E. Savin, M.D., Paris, France, Prof. MUDr. Jarmila Siegelová, DrSc.*

Figure 36: *From the left MUDr. Pavel Homolka, Ph.D., MUDr. Jarmila Matějková, CSc., Prof. MUDr. Jarmila Siegelová, DrSc., head nurse Ludmila Třasoňová, Doc. MUDr. Vladimír Dražil, CSc., nurse Marie Sobková, MUDr. Drahuška Blahová, MUDr. Ilona Dohnalová, CSc. (2000)*

Figure 37: *From the left nurses R. Látalová, T. Slámová, D. Bulová, A. Kotulánová, E. Vránová, head physioterapeutist M. Falberová (2002)*

Figure 38: *Head physioterapeutist Marie Falberová, Prof. MUDr. Jarmila Siegelová, DrSc., Head of the Department, , vice-head MUDr. Jitka Svobodová (2003)*

In 1998, master‘s degree studies in physiotherapy were starting. The first graduates of the bachelor‘s program of Physiotherapy at the Faculty of Medicine continued the studies in the master program.

The study of physiotherapy was coordinated until 1998 by Ing. N. Lžičařová. Since 1998, Mgr. L. Dunklerová has been coordinating the studies in physiotherapy, lectures, practical exercises and clinical training in bachelor‘s and master‘s program studies in physiotherapy.

Mgr. L. Dunklerová in cooperation with prof. MUDr. J. Siegelová, DrSc. ensure repeated accreditation of both forms of study at the level of the Ministry of Health and the Ministry of Education in the Czech Republic.

Figure 39: *First graduates of bachelor‘s degree in physiotherapy in 1998*

Figure 40: *Commission for State Final Examination of the Bachelor‘s Degree 1998, composed of the chairwoman of the commission Prof. MUDr. Jarmila Siegelová, DrSc., Members Doc. MUDr. Ivan Müller, CSc., MUDr. Jana Roubalová, MUDr., Bohumila Müllerová, MUDr. Jitka Svobodová, MUDr. Eva Drápelová, MUDr. František Trkan*

In 1998, a detached workplace for outpatient rehabilitation of the Department of Fuctional Diagnostics and Rehabilitation was opened, including a balneotherapy facility at the Institution of NCO NZO at Vinařská, Brno. For the opening, MUDr. Alena Štětková, CSc., Director of St. Anna Teaching Hospital and the director of NCO NZO MUDr. Petr Svačina, CSc. with the support of the Rector of Masaryk University and Dean of the Faculty of Medicine, significantly contributed by their cooperation to the new establishment.

Figure 41: *From the left MUDr. P. Svačina, CSc., Director of NCO NZO, Prof. MUDr. J. Vorlíček, CSc., Dean of LF MU, MUDr. A. Štětková, CSc., Director of St. Anna Teaching Hospital, Prof. MUDr. J. Siegelová, DrSc., MUDr. J. Svobodová (1998)*

Figure 42: *Staff of the Department 1998*

Figure 43: *From the left MUDr. H. Svačinová, Ph.D., JUDr. J. Jahodářová, MUDr. A. Štětková, CSc., Director of St. Anna Teaching Hospital, MUDr. P. Svačina, CSc., Director of NCO NZO, MUDr. J. Svobodová, Prof. MUDr. J. Siegelová, DrSc., Prof. RNDr. J. Zlatuška, CSC., Rector of MU (1998)*

Figure 44: *From the left M. Penčikovová, MUDr, D. Blahová, Doc. MUDr. V. Dražil, CSc., JUDr. Jahodářová, MUDr. P. Homolka, Ph.D., T. Slámová, E. Vránová, Prof. MUDr. P. Dobšák, CSc., M. Benešová, Doc. MUDr. J. Jančík, CSc. (1998)*

Figure 45: *From the left MUDr. P. Homolka, Ph.D., Prof. MUDr. Z. Placheta, DrSc., head nurse of St. Anna Teaching Hospital, Prof. MUDr. Z. Brázdová, DrSc., Prof. MUDr. J. Zlatuška, DrSc., Rector of MU, MUDr. A. Štětková, CSc., Director of St. Anna Teaching Hospital, Prof. MUDr. J. Vorlíček, CSc., Dean of LF MU, Prof. MUDr. J. Siegelová, DrSc., L. Třasoňová (1998)*

In 2000, the Department of Rehabilitation Care, St. Anna Teaching Hospital was established; its head was MUDr. Jiří Pazdírek (2000 - 2005) and since 2005 until now MUDr. Marcela Nováková; the rehabilitation staff of this facility belonged to the Dept. of Functional Diagnostics and Rehabilitation until 2010; teaching for Bachelor‘s and Master‘s of Physiotherapy was performed there since 2000.

The Department of Functional Diagnostics and Rehabilitation also educated a number of scientific and pedagogical staff of physiotherapy, who achieved Ph.D., habilitation and professor degrees in the field of internal medicine and physiotherapy, not only at Masaryk University, but also at Charles University in Prague.

From 1998 the cardiovascular rehabilitation program of outpatients was realized under Prof. MUDr. Jarmila Siegelová, DrSc. in the Department of Functional Diagnostics and Rehabilitation.

It was one of the results of successful cooperation with Swiss Cardiovascular Center in Bern, Switzerland, led by Prof. H. Saner.

Figure 46: *Prof. Hugo Saner, M.D., Ph.D., Swiss Cardiovascular Center in Bern, Switzerland*

In 2000, rebuilding of the building E, where the Department of Functional Diagnostics and Rehabilitation was situated, under the full activities was realized.

There were built new spaces for cardiovascular rehabilitation and a new lift in the building.

This reconstruction was realized at that time under the head Prof. MUDr. J. Siegelová, DrSc.

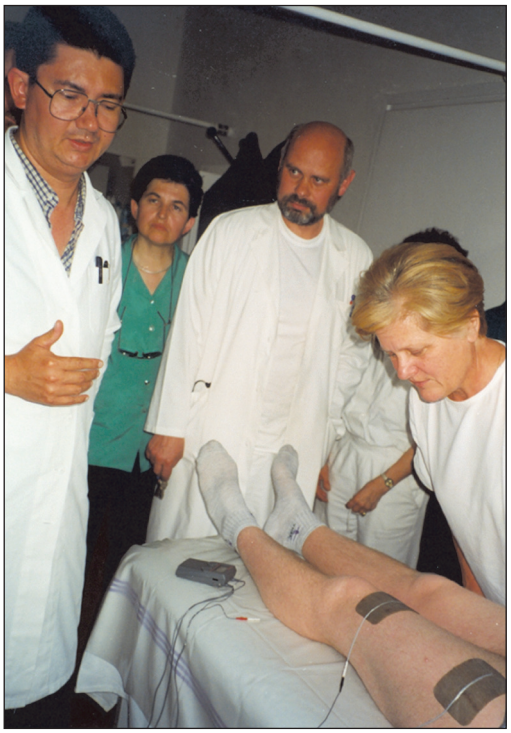

Figure 47: *Dr. J.CH. Eicher, Dijon, France, Doc. MUDr. Jiří Jančík, Ph.D., MUDr. J. Svobodová (2003)*

In 2005, the Department of Physiotherapy and Rehabilitation was established by the management of the Faculty of Medicine of Masaryk University, whose task is to organize and provide teaching in the field of Physiotherapy in Bachelor‘s and follow-up Master‘s Studies.

From 2005 to 2012, Prof. MUDr. Jarmila Siegelová, DrSc. was Head of the Department of Physiotherapy and Rehabilitation of the Medical Faculty of MU. During the academic year, our Department taught students with the aid of about 150 teachers who worked in St. Anna Teaching Hospital and out patients rehabilitation workplaces. Numbers of students fluctuate every year from 180 to 200.

Prof. MUDr. Petr Dobšák, CSc. became Head of the Dept. of Functional Diagnostics and Rehabilitation in 2007.

Prof. MUDr. Petr Dobšák, CSc. started in 1997 as a lecturer, was appointed Associate Professor (habilitated) in 2004 and Professor in 2007; he replaced Prof. MUDr. Jarmila Siegelová, DrSc., who continued in the clinic as a professor.

Vice-head for healing and preventive care of Prof. MUDr. Petr Dobšák, CSc. was first MUDr. Jitka Svobodová, who was replaced later by the vice-head MUDr. Michaela Sosíková, Ph.D. from 2008. The head physiotherapist was Marie Falberová until 2009, from 2009 Mgr. Pavlína Svobodová.

Figure 48: *Prof. MUDr. Petr Dobšák, CSc.,*
Head of Department of Functional Diagnostics and Rehabilitation from 2007 until now
Head of Department of Physiotherapy and Rehabilitation from 2012 until now

Figure 49: *Vice-head MUDr. Michaela Sosíková, Ph.D., from 2008 until now*

Figure 50: *Prof. MUDr. Zdeněk Placheta, DrSc., MUDr. Jitka Svobodová, Marie Falberová, MUDr. Anna Rajdová, MUDr. Michaela Sosíková, Ph.D., MUDr. Pavel Homolka, Ph.D. and staff (2007)*

Figure 51: *Prof. MUDr. Petr Dobšák, CSc., Prof. MUDr. Jan Žaloudík, CSc., Dean of Faculty of Medicine (2007)*

Figure 52: *Marie Falberová, Prof. MUDr. Petr Dobšák, CSc., Prof. MUDr. Jarmila Siegelová, DrSc. (2007)*

In 2010, the Department of Functional Diagnostics and Rehabilitation was renamed to the Department of Sports Medicine and Rehabilitation of Faculty of Medicine, MU, with place of business at St. Anna Teaching Hospital.

In 2012 Prof. MUDr. Petr Dobšák, CSc. became Head of the Department of Physiotherapy and Rehabilitation of LF MU.

Prof. MUDr. Jarmila Siegelová, DrSc. managed the Operational Program „Modifying a system of education in the field of physiotherapy in the field of Education for Competitiveness, funded from European sources, from 2012 to 2014. The project has been successfully completed.

Figure 53: *The research team of the Operational Program in the field of Education for Competitiveness „Modification of the system of education in the field of physiotherapy“*

Department of Sports Medicine and Rehabilitation continues to perform pedagogical training in general medicine (internal medicine), physiotherapy and rehabilitation, teaching together with the Department of Physiotherapy and Rehabilitation.

In 2014, Bachelor‘s program of Physiotherapy was started in English and the first graduates successfully completed their studies in 2017.

In the field of treatment and preventive activities, the Department of Sports Medicine and Rehabilitation performs excellent rehabilitative treatment at the acute beds clinic, at the other clinics of St. Anna Teaching Hospital in Brno, in the field of outpatient treatment and in the field of sports medicine and functional diagnostics of cardiovascular and respiratory diseases.

Figure 54: *First State Final Examination in English: From the left Prof. MUDr. P. Dobšák, CSc., Bc. Eli Odnozopov, Bc. Tessa Bell, Prof. MUDr. J. Siegelová, DrSc., MUDr. E. Drápelová, Doc. MUDr. I. Müller, CSc. (2017)*

Figure 55: *Graduates of the Bachelor's degree in Physiotherapy 2017*

In the field of scientific research, international scientific research projects have been solved together with scientists from Halberg Chronobiology Center, University of Minnesota, USA, Faculty of Medicine, Paris, Dijon, France, Tohoku University of Sendai, University of Tokio, Japan, University of Graz, Austria and other European countries. Detailed information on the scientific publications of the Department of Sports Medicine and Rehabilitation, Masaryk University can be found in the World Databases of Web of Science, Scopus, Medline, Faculty of Medicine, Masaryk University and the Halberg Chronobiology Center, University of Minnesota, USA.

Dr Othild Schwartzkopff (18. 5. 1922 - 23. 5. 2017) Halberg Chronobiology Center University of Minnesota, USA

Jarmila Siegelová, Germaine Cornélissen*

Dept. of Physiotherapy and Rehabilitation, Dept. of Sportsmedicine and Rehabilitation, Faculty of Medicine, Masaryk University, St. Anna´s Teaching Hospital, Brno
**Halberg Chronobiology Center, University of Minnesota, USA*

It is with great sadness for us that Othild Schwarzkopff passed away on May 23, 2017 at the age of 95.

Dr. Othild Schwarzkopff will be remembered as an outstanding clinical physician and from the mid-1990s as a scientist in chronobiology at the Halberg Chronobiology Center in Minnesota, USA.

Dr. Othild Schwartzkopff was born on 18 May 1922 in Germany and received her medical degree in 1946 at the University of Goettingen. After her clinical training in hospital she worked in the Pediatrics Department of the General Hospital in Rheydt / Rheinland and later in the Children's Tuberculosis Institute in Aprath / Rheinland until 1958.

Dr. Othild Schwarzkopff moved to Canada in 1958. She worked in different hospitals and finally she held the position of a pediatric resident at Vancouver General Hospital. She was licensed in British Columbia. In 1963, Dr. Schwartzkopff became a Member of the College of Physicians and Surgeons. In July 1968, she received her license to practice in the USA and moved to Minnesota. Dr. Othild Schwartzkopff became a Fellow of the American Academy of Pediatrics (FAAP) in April 1971. From 1968 to 1988, she was in general pediatric practice in St. Paul, Minnesota, USA. During her last years in practice, she held a clinical academic position in the Pediatrics Department at the University of Minnesota. There as a clinical assistant professor of pediatrics, she introduced second-year medical students to the problems they might face in practice.

In the mid-1990s, Dr. Schwartzkopff joined the Halberg Chronobiology Center, where she served as the Clinical Director. She already had an interest in the cardiovascular system and chronobiology when in 1945, for her dissertation on "The effects of nicotinic acid and nicotinic acid amide on the cardiovascular system, blood pressure in particular". In the field of chronobiology she measured the blood pressure at about the same time each day, covering usually at least a week on each patient. She provided also ambulatory blood pressure monitoring on herself over some years. She collected also data that are now of interest in a transverse way for looking at about half-weekly and weekly components of biological rhythms in healthy subjects and patients. As part of the BIOCOS Project, Othild Schwarzkopff has indeed participated in many studies, with collaborators around the world, as attested by her over 270 publications and her numerous invitations to lecture abroad, notably here in Brno, but also in Austria, China, India, Russia, Saudi Arabia, Slovakia, Taiwan, Turkey and Vietnam, among others. She visited our Masaryk University very often together with prof. Franz Halberg and she presented new results in chronobiologic studies. Some scientific presentations were in every year organized by Jarmila Siegelova as MEFA Congresses in Brno, in Noninvasive Methods of Cardiology Congresses, in Workshops in Masaryk University. On the personal contact she discussed the chronobiology question with the other regular partipitans in Congresses in Masaryk University in Brno, namely with prof. Dr. Thomas Kenner, D.h.c. mult,, Rector emeritus of University in Graz, Brigitte Kenner, late Prof. Dr. Jean Paul Martineaud, Faculty of Medicine, Paris, late Prof. Dr. Bohumil Fiser, Masaryk University, Minister of health (2000-2002) in Czech Republic and our scientific team (Dr. Jiri Dusek and prof. Siegelova) from Masaryk University. From 2011, she took part in every

year scientific Workshops and Congresses with International participation via video-transmission. In 2008 Dr. Othild Schwartzkopff was presented at the proclamation of Brno consensus of Vascular Variability Disorders. Prof. Franz Halberg proposed this evaluation based on over 61 years lasting chronobiologic scientific studies on blood pressure and heart rate, together with professor Germaine Conelissen, Dr. Othild Schwarzkopff and in cooperation with chronobiologists around the world and Dr. Othild Schwartzkopff was a hard working woman, with great organizational abilities, who was able to manage the social life in the laboratory environment, home hospitality, offered for the scientist who visited the Halberg Chronobiology Center and an excellent scientist and medicine doctor.

Prof. Franz Halberg and Dr. Othild Schwarzkopff, together with prof. Germaine Cornelissen, give very important message, which reflects that one of the important tasks of the Halberg Chronobiology Center is the prevention of cardiovascular diseases, namely to screen blood pressure and heart rate for Vascular Variability Anomalies, and while using the information from longitudinal records to learn more about influences from our environment near and far, striving for a unified science.

The paper is amplified from: Cornelissen G, Beaty L, Siegelova J, Otsuka K, Watanabe Y, Singh RK, Singh R, Singh RB, Kenner B, Kenner T. Obituary: Dr. Othild Schwartzkopff: 18 May, 1922 – 23 May 2017. World Heart J 2017; 9 (2): in press.

Figure 1: *Dr. Othild Schwarzkopff 18. 5. 1922 - 23. 5. 2017*

Figure 2: *Professor Franz Halberg, Dr. Othild Schwartzkopff during MEFA Congress in Brno 2005 organized by Prof. MUDr. Jarmila Siegelová, DrSc.*

Figure 3: *Dr. Othild Schwartzkopff during Noninvasive Methods in Cardiology Congress in Brno 2002*

Figure 4: *Dr. Othild Schwartzkopff with Brigitte Kenner, Dr. Jiri Dusek and Prof. MUDr. Jarmila Siegelová, DrSc., Casle Rájec near Brno, Congress Noninvasive Methods in Cardiology, October 2005*

Figure 5: *Professor Bohumil Fišer, As. Professor Michal Pohanka, Professor Thomas Kenner, Brigitte Kenner, Dr. Othild Schwartzkopff , Professor Franz Halberg, Dr. Jiří Dušek, Professor Jarmila Siegelová, Brno Congress Noninvasive Methods in Cardiology, 2008 (Brno Consensus)*

Figure 6: *Othild Schwartzkopff, M.D., prof. Franz Halberg, M. D., Dr. h. c. multi., Prof. MUDr. Jarmila Siegelová, DrSc., Dr. Jiri Dusek, Brigitte Kenner, Prof. Thomas Kenner, M. D., Dr. h. c. multi., Austria – videoconference in Brno Masaryk University, 2012*

Figure 7: *Professor Franz Halberg, Dr. Othild Schwartzkopff, Professor Germaine Cornélissen in Halberg Chronobiology Center University Minnesota on May 3-4, 2013 during Symposium (videoconference) in Masaryk University Brno with participation of Professor Kenner and Brno team from Department of Physiotherapy and Rehabilitation*

Figure 8: *Dr. Othild Schwartzkopff at the site of Battle at Austerlitz near Brno, 2004*

The Meaning of Acute Changes of Cardio Ankle Vascular Index

Kazuhiro Shimizu[1], MD. PhD. Akihiro Ogawa[2], PT. MSc. and Kohji Shirai[1], MD. PhD.

[1]Department of Internal medicine, Toho University Sakura Medical Center, Japan
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Key word

CAVI, Arterial stiffness

Summary

The cardio-ankle vascular stiffness index (CAVI) reflected vascular aging, and the progression of atheroscrlosis. Furthermore, CAVI was observed to change relatively short term. When nitroglycerin was administered, CAVI decreased in five minutes, indicating CAVI reflected the state of arterial smooth muscle cell contraction. We observed that CAVI of the people living 300 km far away from the center of big disaster of earthquake and tsunami, increased rapidly. And after that, the incidence of brain hemorrhage and death rate increased in the town. We also observed the several cases whose suffered from coronary artery disease, or aortic dissection and brain hemorrhage, increased CAVI just before those accidents. In considering those, we proposed the hypothesis “the smooth muscle contraction theory for the vascular accident”. Here, we want to discuss the meanings of rapid changes of CAVI.

Introduction

In 2006, a new arterial wall stiffness parameter, the cardio-ankle vascular stiffness index (CAVI), was developed. CAVI is a parameter that reflects the stiffness of the aorta, femoral artery, and tibial artery as a whole. (1) The conspicuous feature is independency from blood pressure at measuring time. The stiffness shown by CAVI was thought to comprise organic stiffness and functional stiffness. Organic stiffness is mainly concerned with collagen, elastinhyaluronic acid, calcification and intimal thickening with smooth muscle cell proliferation, whereas functional stiffness is mainly due to smooth muscle cell contraction (Fig 1). In this paper, to understand the meaning of rapid changes of CAVI, the effect of nitroglycerin administration, and the changes of CAVI of the people suffering from huge earthquake, and those of several case sufferings from cardio-vascular events were studied. Finally, we discussed those results and presented the new hypothesis for the occurrence of cardiovascular events.

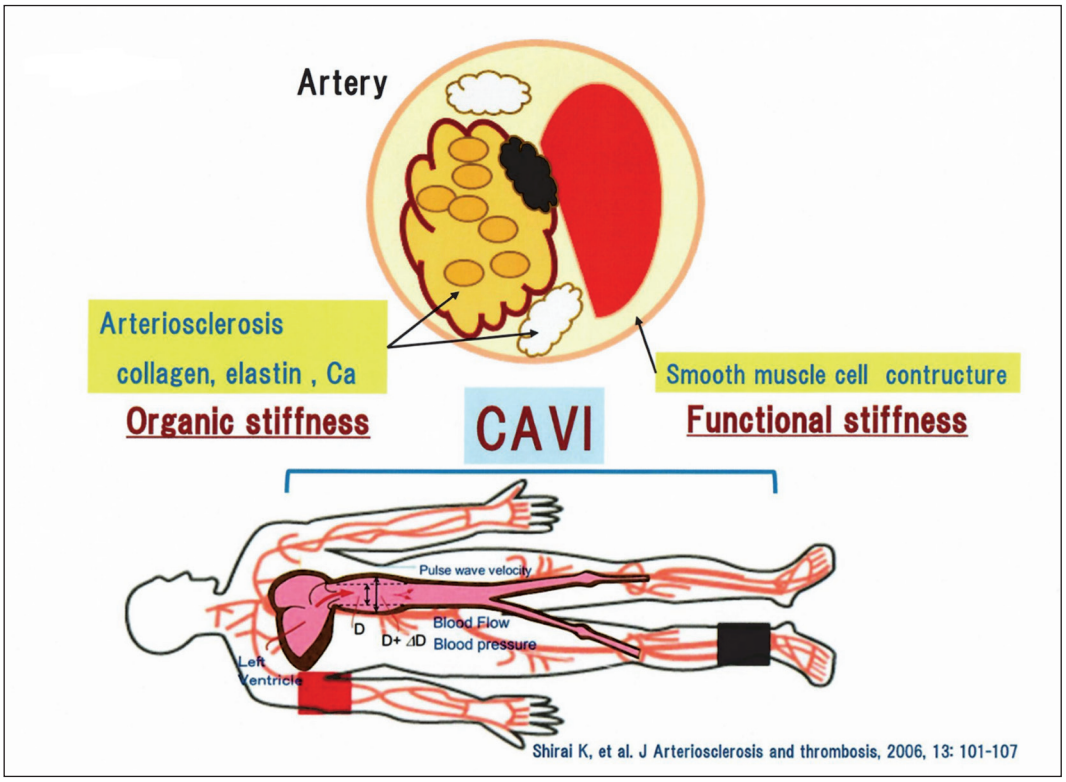

Figure 1: *CAVI detect the organic stiffness and the functional stiffness*

I. Effect of nitroglycerin administration on cardio-ankle vascular index. As shown in Fig. 2, we reported that arterial stiffness shows acute changes by nitroglycerin (NTG) for both healthy people and atherosclerotic people. After resting for 10 minutes in supine position on a bed, CAVI was measured at baseline. Next, a tablet of NTG (0.3mg) was administered sublingually and CAVI was measured every 5 minutes for 20 minutes using a Vasela 1500 (Fukuda Denshi, Tokyo, Japan). Simultaneously, BP and heart rate (HR) were measured by Vasela 1500.

The purpose of this study was to clarify the difference between effects of NTG on the functional stiffness in patients with and without coronary artery disease (CAD) using CAVI.

To date, several reports have discussed the effect of NTG on arterial stiffness using PWV. However, as shown in the current study, BP decreased after NTG administration. Thus, even when PWV decreased, it cannot be concluded that NTG actually decreased the arterial stiffness, because PWV decreases when the BP decreases. 1 On the other hand, CAVI is independent from BP at the time of measurement. Taken together, the effect of the drugs which affect BP on the proper arterial stiffness can be evaluated using CAVI. In this study, CAVI decreased in both healthy young adults and in CAD patients after NTG administration. This is the first report to demonstrate the effect of NTG on proper arterial stiffness of the artery, in vivo.

CAVI at the baseline might indicate the state of organic stiffness as atherosclerosis. After taking NTG, decreased CAVI (ΔCAVI) might indicate relaxation of smooth muscle cell contraction. In another words, functional stiffness might be due to the state of contracture of arterial smooth muscle cells.

After NTG administration, the stiffness of the arteries from the origin of the aorta to the ankle as measured by CAVI decreased in both healthy volunteers and CAD patients by nearly the same extent, suggesting that the response of the arterial smooth muscle cell to nitric oxide is preserved even in CAD patients under medications.

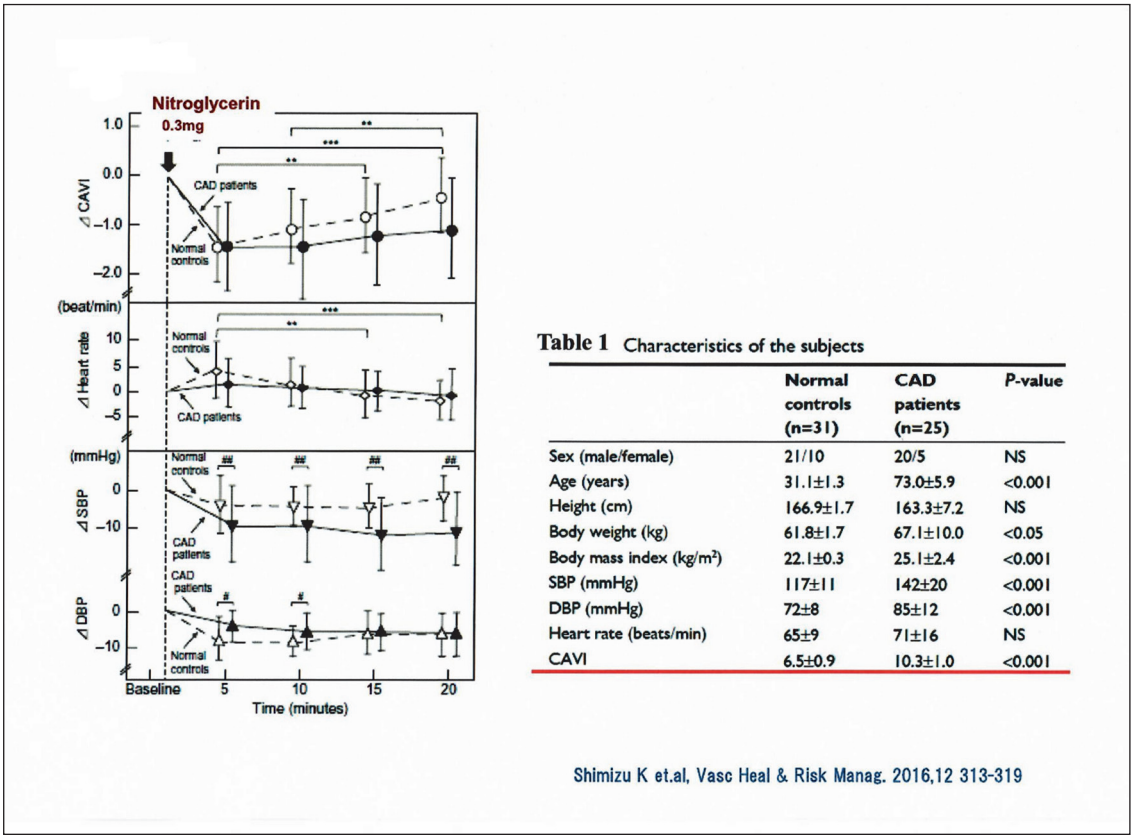

Table 1 Characteristics of the subjects

	Normal controls (n=31)	CAD patients (n=25)	*P*-value
Sex (male/female)	21/10	20/5	NS
Age (years)	31.1±1.3	73.0±5.9	<0.001
Height (cm)	166.9±1.7	163.3±7.2	NS
Body weight (kg)	61.8±1.7	67.1±10.0	<0.05
Body mass index (kg/m²)	22.1±0.3	25.1±2.4	<0.001
SBP (mmHg)	117±11	142±20	<0.001
DBP (mmHg)	72±8	85±12	<0.001
Heart rate (beats/min)	65±9	71±16	NS
CAVI	6.5±0.9	10.3±1.0	<0.001

Shimizu K et.al, Vasc Heal & Risk Manag. 2016,12 313-319

Figure 2*: The effect of nitroglycerin administration to CAD patients and healthy people*

II. A huge earthquake hardened arterial stiffness monitored with CAVI. It is known that the frequency of cardiovascular events increases just after a huge earthquake.

On March 11th, 2011, an earthquake of magnitude 9.0 occurred on the Pacific coast of Tohoku, Honshu Island, Japan, at 14:46 local time (the Great East Japan Earthquake). It was followed by a series of powerful aftershocks, with 31 earthquakes of magnitude larger than 6 in 3 days. As shown in Figure 1, our institute (Toho University Sakura Medical Center Hospital) was situated about 300 km away from the epicenter. The building was strongly shaken, and part of a wall collapsed. An unusual crisis occurred in our town. Shimizu et al. reported that arterial stiffness was increased by psychological stress (Fig 3). Psychological stress caused the increase of death (Fig 4).

The Great East Japan Earthquake provided an unusual opportunity to investigate the relationship between emotional stress and arterial stiffness. The Great East Japan Earthquake increased CAVI-monitored arterial stiffness in both healthy people and patients with cardiovascular risk factors, whereas blood pressures did not change significantly. We investigated the incidence of death rates in our town. As shown in Fig. 4, the number of deaths in our town in the following month (April 2011) increased compared with that in April during several previous years. And the number of patients, who were hospitalized into our hospital with acute coronary syndrome, takotsubo cardiomyopathy, and cerebral bleeding just after the earthquake. The acute increase in arterial stiffness might be an important risk factor for cardiovascular morbidity and mortality after a big disaster. This finding could play a key role in solving the cause of cardiovascular events after a disaster.

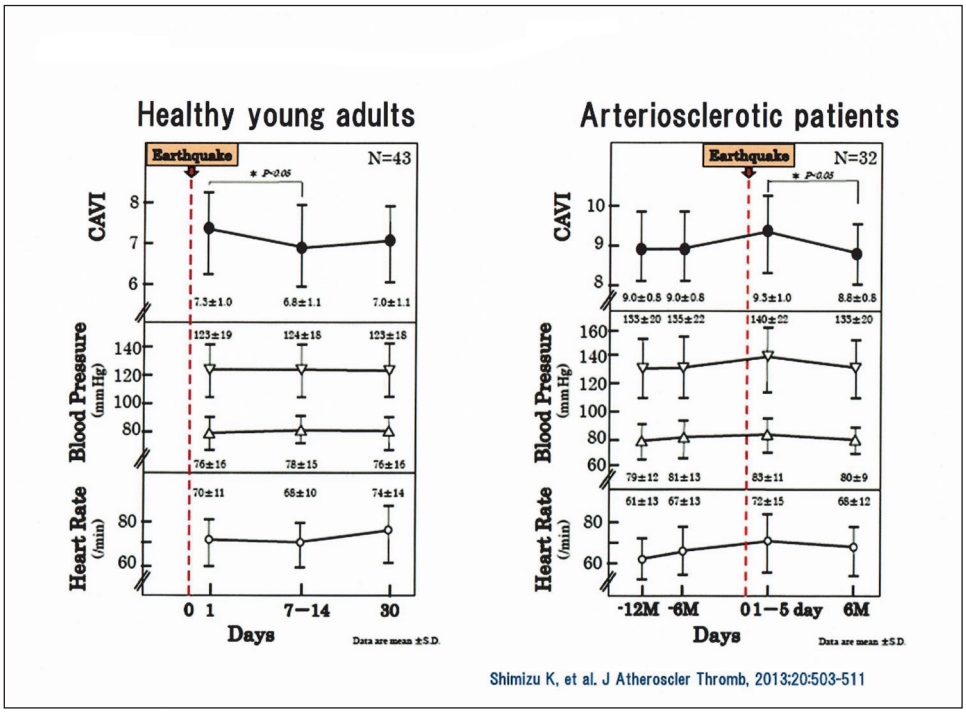

Figure 3: *A huge earthquake hardened arterial stiffness monitored with CAVI*

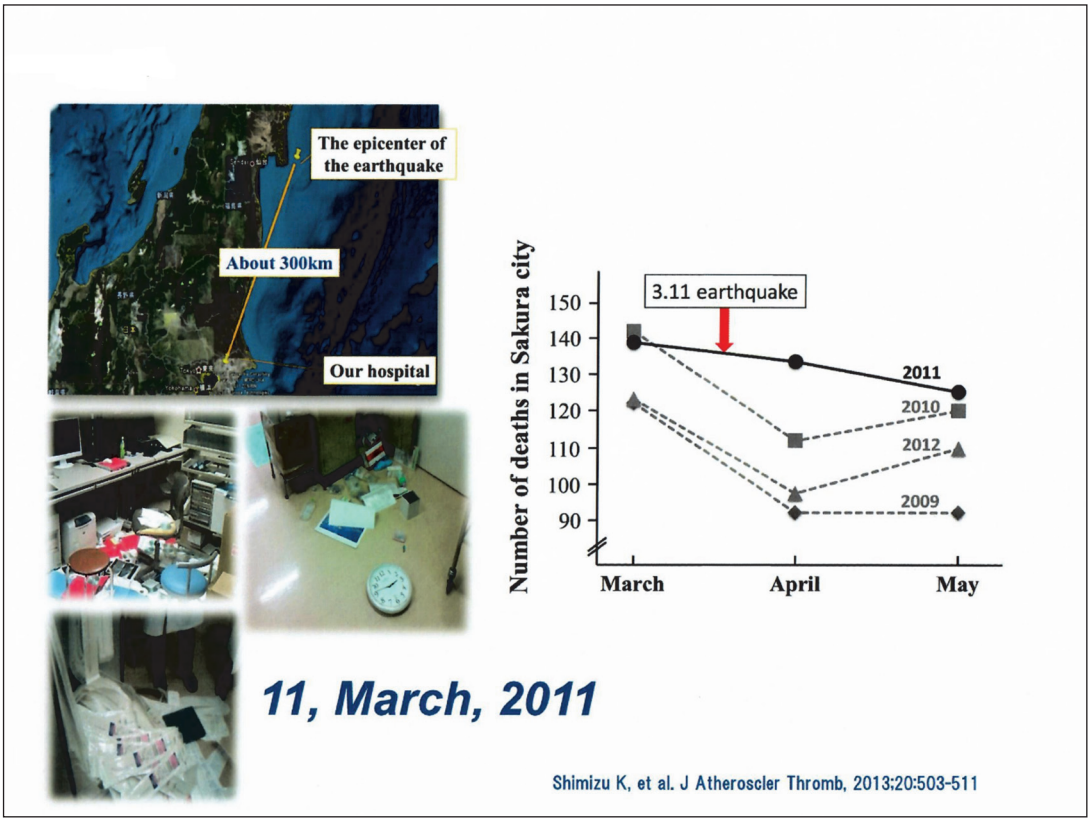

Figure 4: *Psychological stress caused the increase of death*

III. The changes of CAVI in patients suffering from cardio-vascular events.

We met several cases whose CAVI was enhanced relatively short term, and suffered from cerebral infarction, dissecting aneurysm, acute myocardial infarction and cerebral bleeding (Fig 5). Those might just happen by chance. But, there might remain some possibility that this is not by chance, but by some causal relationship. The latter possibility will discussed in the next chapter.

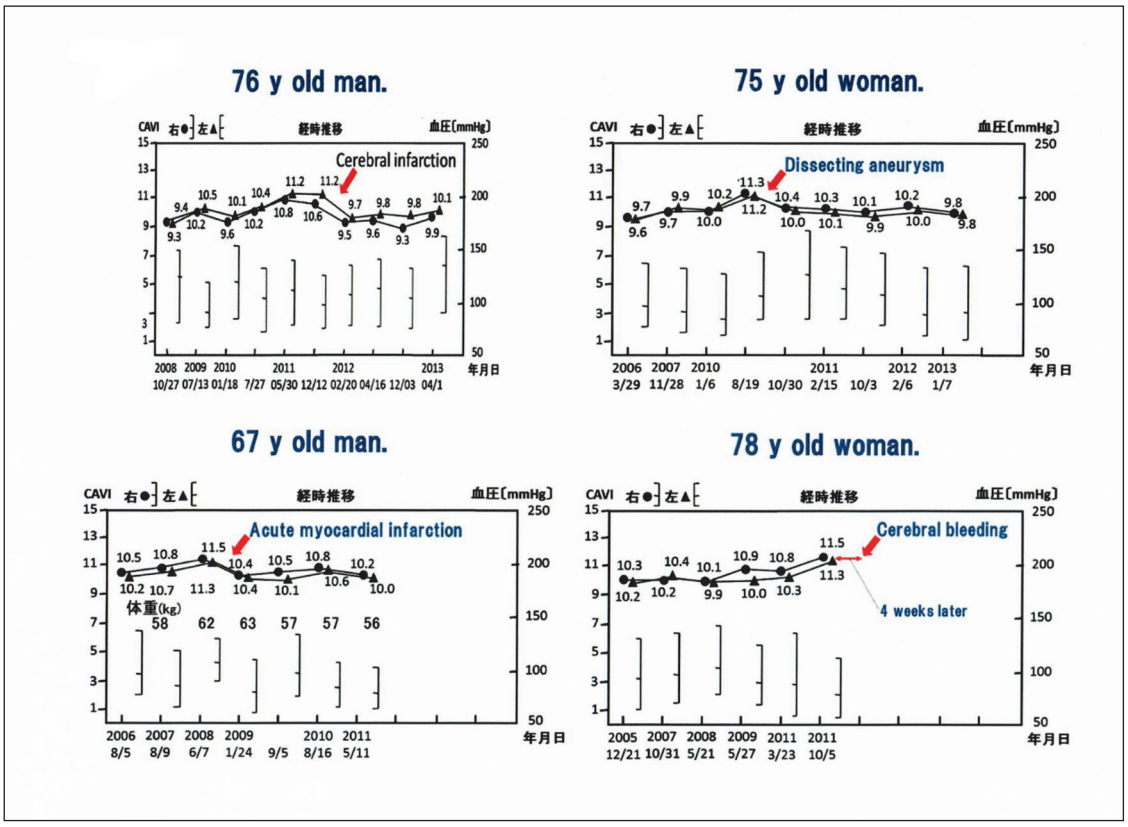

Figure 5: *ΔCAVI raise might be a sign of cardiovascular events in the near future*

IV. Arterial smooth muscle cell contraction theory for the occurrence of cardio-vascular events

To explain the process that enhanced ΔCAVI just before the cardiovascular events, might be the trigger of following cardio-vascular events, we considered arterial smooth muscle cell contraction theory for the occurrence of cardio-vascular events as illustrated in Fig 6.

Atherosclerotic changes occurred mainly in intimal layer. In this process, organic stiffness was increased. That was reflected to enhanced CAVI. At this stage, vasa vasorum were developed in atheromatous lesion from the adventitia and penetrated medial smooth muscle layer. Thus, nutrition in atheromatous lesion was supplied by vasa vasorum. When CAVI was enhanced further in relatively short term, this means that medial smooth muscle cells begin to contract and to choke the vasa vasorum. Then, atherosclerotic lesion become ischemic state, and easily undergo necrosis. Then, plaque rupture, dissecting aneurysm and hemorrhage occurred from this necrotic core.

Based on this theory, continuous monitoring CAVI might be very important and useful predictor of cardiovascular events. To prove this hypothesis, we are now under investigation from various aspects.

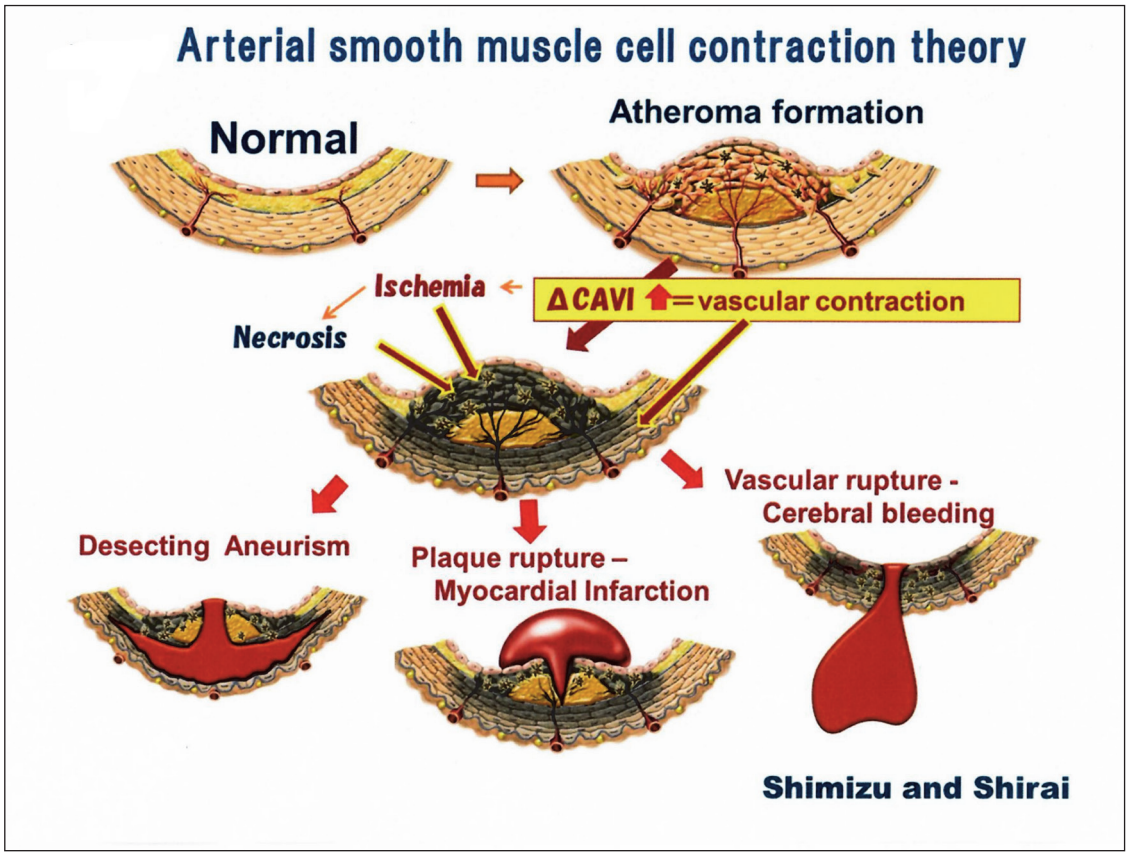

Figure 6: *Arterial smooth muscle cell contraction theory*

Conclusion

CAVI is not only a good surrogate marker of atherosclerosis, but also a good moritoring index of life style-related diseases such as hypertension, diabetes mellitus, dyslipidemia, visceral obesity. Furthermore, enhanced CAVI during continuous monitoring might be an advance warning for the cardiovascular events.

Acknowledgement

We deeply appreciated prof. PETR DOBSAK and prof. JAMILA SIEGELOVA.

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Acute Effect of Resistance Training on Cardio-Ankle Vascular Index (Cavi)

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[1] Department of Rehabilitation, Toho University Sakura Medical Center, Japan
[2] Department of Internal medicine, Toho University Sakura Medical Center, Japan

Key words

Cardio-ankle vascular index, arterial stiffness, resistance training, atherosclerosis,

Introduction

Pulse wave from the heart is very important role of our homeostasis. Therefore elasticity of the aorta plays an important role to keep vascular functions. Vascular dysfunction has been shown to play a central role in arteriosclerosis. Cardio-Ankle Vascular Index (CAVI) makes it possible to determine non-invasively arteriosclerosis 1). Dobsak et al. reported that CAVI was significantly improved by 12 weeks exercise and muscle contraction stimulation for heart failure patients. However, there is no report about the immediate change of the CAVI after resistance training2). The aim of this study was to investigate correlation about functional stiffness and skeletal muscle mass after resistance training (RT).

Subjects

The subjects were 21 healthy adult males (Table 1).

Table 1: *Characteristic of experimental subjects*

Healthy male	N=21
Age (years old)	28.3±7.3
Height (m)	1.75±0.1
Weight (kg)	70.5±12.7
BMI	23.5±3.7

Methods (experimental methods and design)

The study was conducted in a quiet environment and temperature-controlled room (25°C–26°C). The subjects were examined at approximately the same daytime after a standardized light meal and

were asked to avoid caffeine or tobacco on the day of the study. At baseline, CAVI was measured in supine position after 10min rest. Next, all the subjects performed 10-times of RT exercises on right leg. Then, CAVI was measured immediately after RT and 5min later (Figure 1).

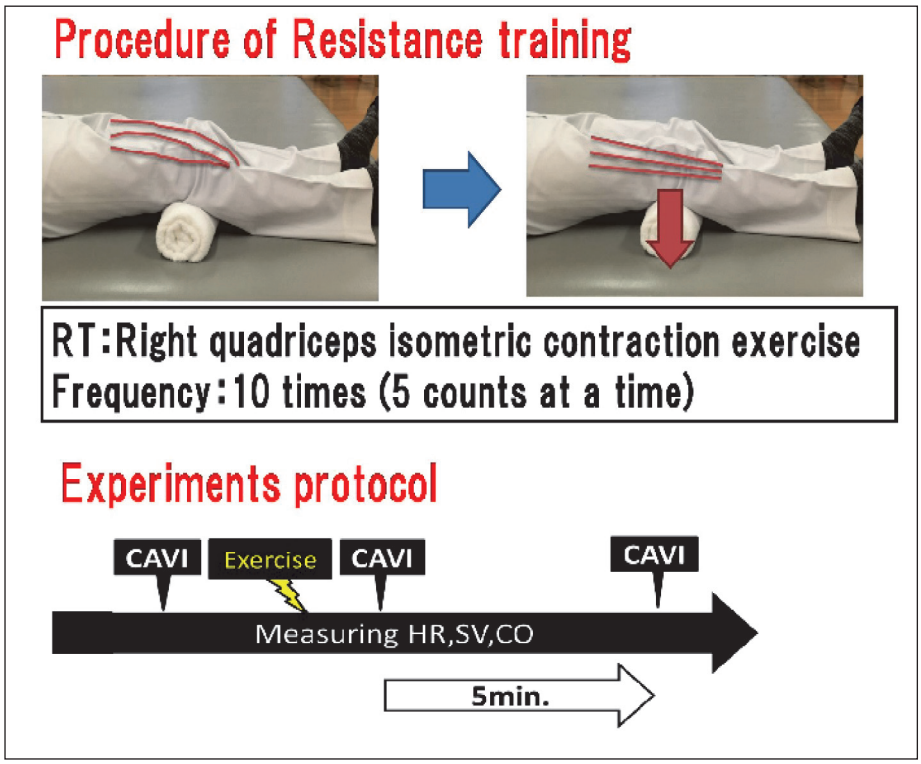

Figure 1: *Procedure of resistance training and experimental protocol*

CAVI was measured using device VaSera® 1500 (Fukuda Denshi Co., Ltd, Tokyo, Japan). The changes of stroke volume (SV) and cardiac output (CO) were continuously monitored using hemodynamic monitoring system Aesculon® (Osypka Medical, California, USA). The evaluation of skeletal muscle mass and body composition was done by bioelectrical impedance analyzer Inbody® 770 (Inbody Co., Ltd., Seoul, South Korea). Skeletal muscle mass index (SMI) was calculated using limb skeletal muscle mass and body height as follows:

$$\textbf{SMI = limb skeletal muscle mass / height (m)}^2$$

Statistics

Each parameter was evaluated from three measurements using Friedman test. In the case of significant difference; Steel-Dwass test was used for post hoc multiple comparisons. Mann-Whitney test was used to compare change of CAVI (ΔCAVI) for difference between right (Rt) and left (Lt) value of CAVI. Relationship between CAVI and SMI was examined by partial correlation adjusted for age. Significance level was set at $P<0.05$. SPSS Statistics (version 21) was used for data analysis.

Results

Continuous measurement by impedance cardiography showed that HR was increased until the end of RT. HR peaked within 30sec after the end of RT, and then decreased. On the other hand, there was no obvious change in the SV. Thus, the change in CO was dependent on HR (Figure 2).

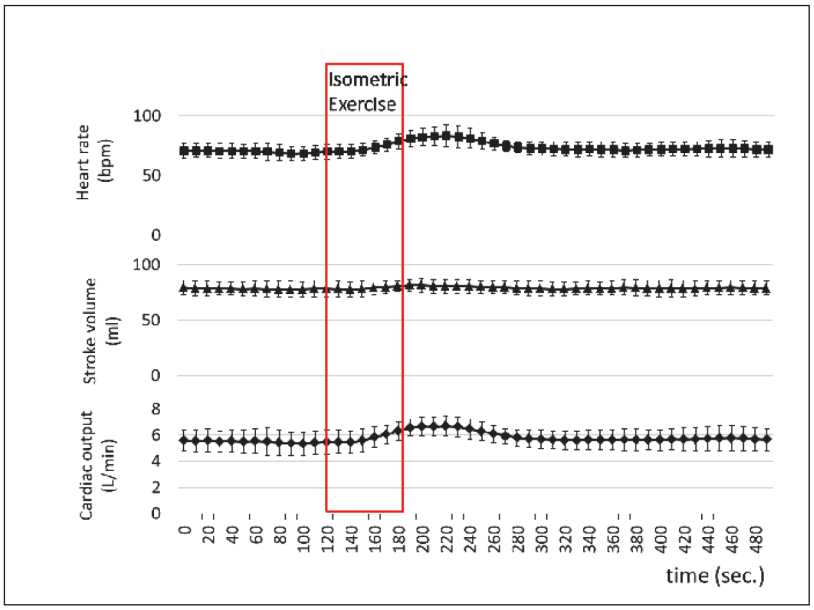

Figure 2: *Changes in cardiac output*

There was no significant change in either diastolic and systolic blood pressure (Table 2).

Table 2: *Changes in blood pressure at each measurement time*

		BL	RT	5min	p
SBP (mmHg)	Arm	125.0 (118.0,130.0)	123.0 (120.8,133.8)	122.5 (118.0,133.3)	n.s.
	Rt Ankle	136.5 (127.3,148.5)	137.0 (131.0,143.0)	135.5 (128.5,142.5)	n.s.
	Lt Ankle	140.0 (130.0,148.5)	138.0 (130.8,144.5)	135.5 (125.0,144.3)	n.s.
DBP (mmHg)	Arm	79.5 (71.8,81.0)	77.5 (71.3,83.0)	77.0 (72.0,84.3)	n.s.
	Rt Ankle	76.0 (67.8,81.3)	75.0 (68.8,79.0)	76.0 (70.0,79.3)	n.s.
	Lt Ankle	78.0 (71.8,81.5)	75.5 (68.0,80.5)	77.5 (72.5,80.3)	n.s.

Friedman test Median(quartile) n.s.: no significant

CAVI in both Rt (exercise side) and Lt (non-exercise side) decreased significantly after RT (6.00 vs. 5.80, P<0.01; 6.00 vs. 5.80 P<0.01, respectively), and returned to the CAVI value registered at baseline after 5min (5.80 vs. 6.00 P<0.01; 5.70 vs. 6.00 P<0.01, respectively). This result is shown in Fig.3. There was no significant difference in the ΔCAVI between Rt and Lt (Table 3). Both Rt and Lt CAVI and SMI showed significant negative correlation (r=-0.59; P<0.05). This result is shown in Fig.4.

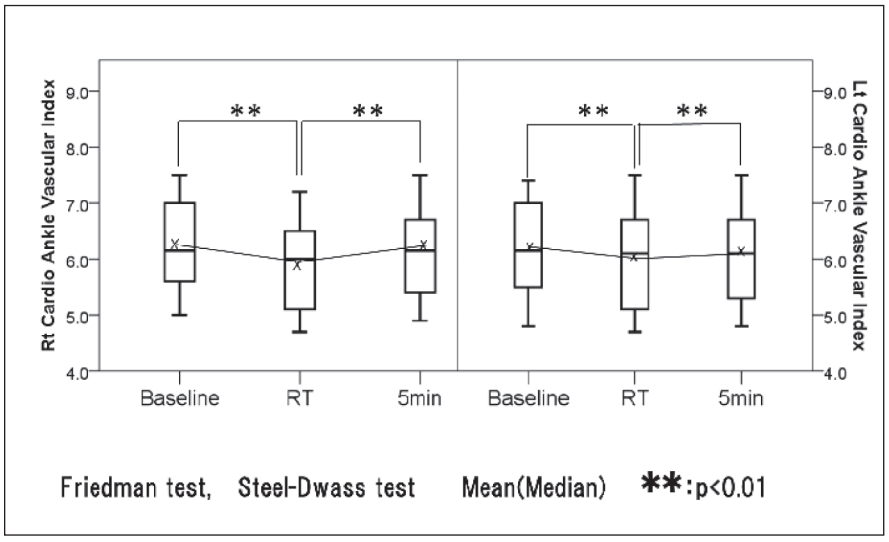

Figure 3: *Changes in CAVI at each measurement time*

Table 3: *Comparison of ΔCAVI*

ΔCAVI	Rt (RT side)	Lt (non-RT side)	p
RT - Baseline	-0.30 (-0.53 , -0.18)	-0.30 (-0.40,-0.80)	n.s.
5min - RT	0.20 (0.10,0.45)	0.15 (0.00,0.30)	n.s.
5min - Baseline	-0.05 (-0.23,0.00)	-0.05 (-0.20,0.00)	n.s.
Mann-Whitney test	Median(quartile)	n.s.: no significant	

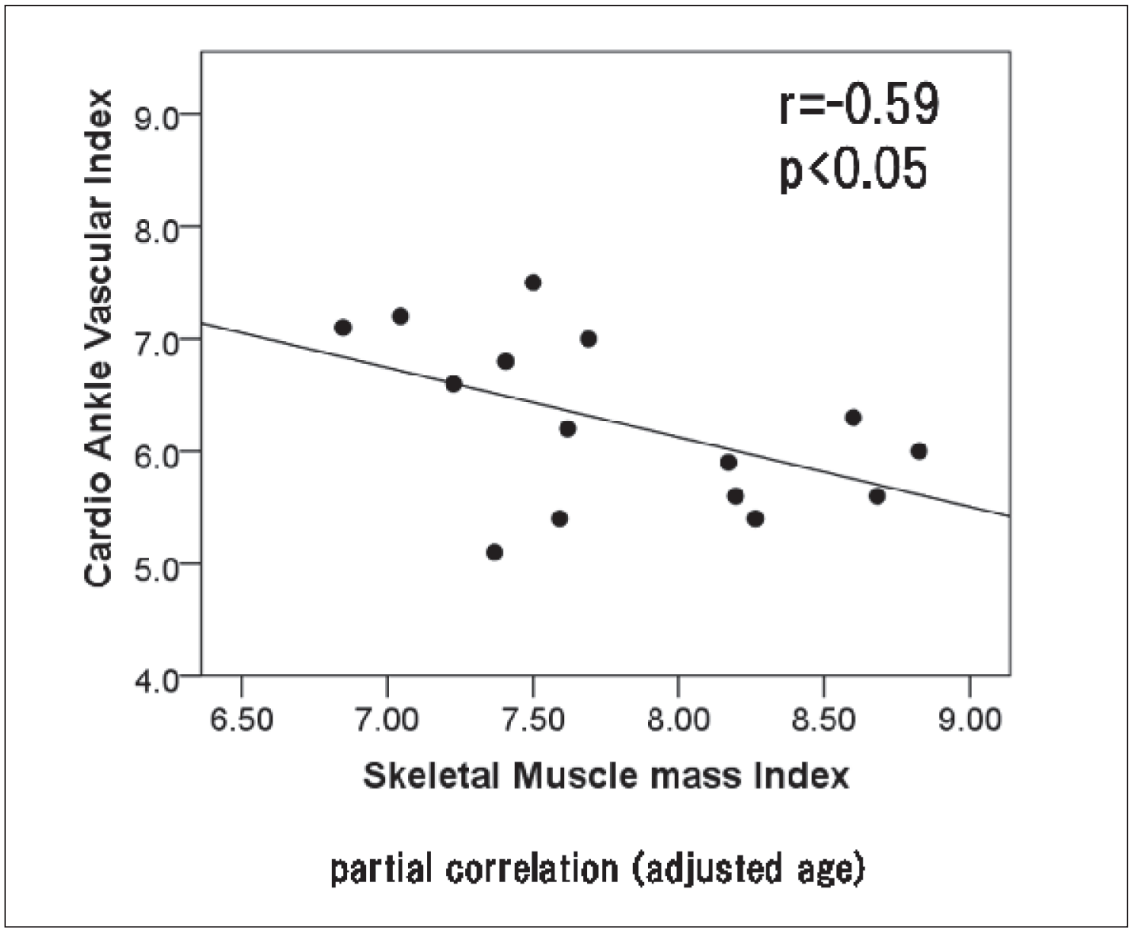

Figure 4: *Relevance of CAVI and SMI*

Discussion

This study analyzed the acute change of CAVI before and after a bout of resistance training. Similar changes were observed on both exercising and non-exercise side. One previous trial reported that CAVI was reduced immediately after aerobic exercise (3), and in the present study we found similar results. However, our study brought a new insight because the CAVI changes were promoted by resistance training (and in one leg only). This observation might demonstrate the systemic effect of nitric oxide (NO) activation by exercise (4). Shimizu et al. (2016) showed similar changes of CAVI after administration of nitroglycerin (5). There was also the relevance between CAVI and SMI. Sampaio et al. (2014) found a decreased SMI and increased CAVI in a group of community-dwelling elderly, where CAVI was shown to be an independent factor of skeletal muscle mass (6). It is likely that vascular elastic function plays an important role in blood flow of skeletal muscles. The present study has several limitations. First, all involved subjects were healthy males, and not patients with cardiovascular diseases. Secondly, due to technical limitations, it was not possible to measure the changes of nitric oxide production.

Conclusion

Increased peripheral blood flow promoted by isometric contractions, can improve the systemic vascular functional stiffness. The present study showed that partial (one-leg) resistance training may contribute to the decrease of vascular stiffness. From this point of view, this study has fundamentally contributed to clarify the effect of exercise on vascular functional stiffness.

Acknowledgement

We deeply appreciated the assistance from Professor Petr Dobsak and Professor Jarmila Siegelova.

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Different Chronotherapy Protocols Applied to Blood Pressure

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Dedicated to the memory of Franz Halberg

Abstract

Blood pressure serves both as a marker variable and as a gauge of the response to timed treatment (chronotherapy). The relative merits of several transverse and longitudinal chronotherapy designs are reviewed herein, from small studies on groups and N-of-6 pilot studies to larger clinical trials. Some chronotherapy designs are aimed at optimal results for the average patient in a given target population, while others aim at personalized chronotherapy, where each patient in the study is considered as an N-of-1 pilot. All chronotherapy trials considered herein relied on around-the-clock blood pressure measurements obtained automatically to determine optimal treatment times. Because anti-hypertensive medications can affect the circadian amplitude in addition to the rhythm-adjusted average (MESOR), treatment effects should be assessed on all characteristics of the circadian blood pressure rhythm. Because abnormal blood pressure and heart rate variability also relates to cardiovascular disease risk, anti-hypertensive treatment should target not only the lowering of blood pressure, but also the restoration of an acceptable circadian variation in blood pressure. Methods to analyze individual blood pressure records makes it now feasible to determine personalized optimal treatment times. Outcome studies remain to be performed to assess the gain to be obtained from personalized chronotherapy in terms of an actual decrease in adverse cardiovascular events.

Keywords

Blood Pressure, Blood Pressure Variability, Chronotherapy, Circadian, Cosinor, Longitudinal versus Transverse Design, Response Rhythm, Vascular Variability Disorders

Introduction

Circadian rhythms are in the spotlight now that a molecular basis has provided a mechanism for their existence, the importance of which has just been recognized by the Nobel Assembly at the Karolinska Institutet that awarded the 2017 Nobel Prize in Physiology or Medicine jointly to Jeffrey C. Hall, Michael Rosbash and Michael W. Young "for their discoveries of molecular mechanisms controlling the circadian rhythm".

The term "circadian", derived from the Latin "circa" (about) and "dies" (day), was coined in 1959 by Franz Halberg to indicate that circadian rhythms had a period of about 24 hours [1]. The meaning of the term refers to free-running and the partly endogenous nature of circadian rhythms, their period differing slightly but statistically significantly from 24 hours in the absence of environmental time cues

[2, 3]. It also indicates the statistical uncertainty in estimating the period: even under synchronized conditions, circadian characteristics, including the period, cannot be estimated exactly, because of measurement error and changes occurring from one day to another, as amply documented for blood pressure [4, 5].

As shown by Halberg, circadian rhythms are ubiquitous; they characterize most, if not all, variables across species, from archaea [6] to humans. In particular, his demonstration of circadian variation in mitoses of different organs and tissues, and for different liver functions related to different stages of the cell cycle, laid the foundation for cancer chronotherapy [7]. Broader applications followed his demonstration of the hours of changing resistance to a host of external stimuli [8-13]. The physiological response to stimuli (such as noise, bacterial endotoxins, radiation, and drugs) changes predictably as a function of circadian stage. It is thus possible to optimize treatment by timing its administration in order to maximize its effectiveness while minimizing its side effects. This is the principle underlying timed treatment (chronotherapy).

Chronotherapy can make the difference between life and death

Timing, the critical ingredient of chronobiological designs, is not just another factor that can be ignored. Under the standardized conditions of the laboratory, timing was repeatedly shown to tip the scale between health and disease, and even between death and survival. This is the case for instance in relation to the exposure of mice to the same dose of an adrenal cortical inhibitor (SU-4885) as a function of circadian timing. In three experiments involving 70, 210, and 350 mice, tested at 6 different circadian stages 4 hours apart in relation to the lighting regimen of 12 hours of light alternating with 12 hours of darkness, depending on the dosage, most if not all mice died when exposed late during the light (rest) span, but most if not all survived when exposed to the same dosage of the same agent earlier during the rest span, Figure 1.

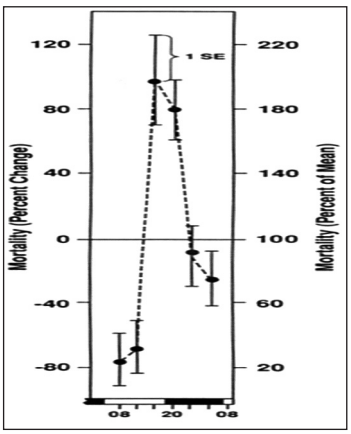

Figure 1: *In the experimental laboratory, inbred animals of the same strain, sex and age, receiving the same dose of the same drug administered at one of 6 different circadian stages can either all survive or all die, depending only on when the drug was administered. Timing is as important, if not more important than dosing. © Halberg Chronobiology Center*

The response to a single daily "meal" can also make the difference between life and death in a mammalian model of potentially fatal interactions between hunger, cold and rhythms, namely the singly-housed mouse abruptly restricted to a single daily "meal". Most singly-housed mice (but not multiply-housed mice) die when they have access to food for 4 hours during the first part of the light (rest) span each day, but if food is only available during 4 hours in the early part of the dark (active) span, most of the mice survive [14].

Blood pressure and blood pressure variability

Blood pressure varies greatly. It is characterized by a large-amplitude circadian rhythm in both normotensive and hypertensive individuals [15, 16]. Circadian rhythm characteristics also usually undergo large day-to-day variability [4, 5]. Abnormal variability patterns of blood pressure and heart rate have been associated with an increased cardiovascular disease risk in several outcome studies, beyond an elevated blood pressure itself [17, 18].

The circadian pattern of blood pressure, described by its rhythm-adjusted mean value, the MESOR (Midline Estimating Statistic Of Rhythm), its double amplitude and acrophase, measures of the predictable extent and timing of change within 24 hours, and its waveform, determined by characteristics of harmonic terms, also differs between men and women, and undergoes predictable changes as a function of age [19]. It thus made sense to derive time-specified reference limits (chronodesms) computed as circadian-stage-dependent 90% prediction limits computed on the basis of data collected from clinically healthy peers, separately for men and women in different age groups. Similarly, 90% prediction limits were derived for each circadian parameter. A patient's record can thus be compared to these chronobiologic standards to determine whether the blood pressure profile is within acceptable limits or not, based on both the 2-component cosinor model fitted to the data and on a computer-comparison of the patient's record versus the chronodesmic limits of clinically healthy peers matched by gender and age. Instead of the usual question whether blood pressure is too high or acceptable, more informative questions can be answered, such as "for how long is blood pressure above the upper limit of acceptability", "what is the total amount of blood pressure excess" (estimated as the area delineated by the record when it exceeds the time-specified upper 95% prediction limit and that limit), and "when does most of the blood pressure excess occur" [20]. This approach by "sphygmochron" [20] goes beyond the concept of the blood pressure load [21], as illustrated in Figure 2. Whereas both patients have a similar percent time elevation (or blood pressure load versus time-specified limits), blood pressure excess (or hyperbaric index, HBI) is more than three times larger for patient #2 than for patient #1 (764 vs. 231 mmHg x hour over 24 hours).

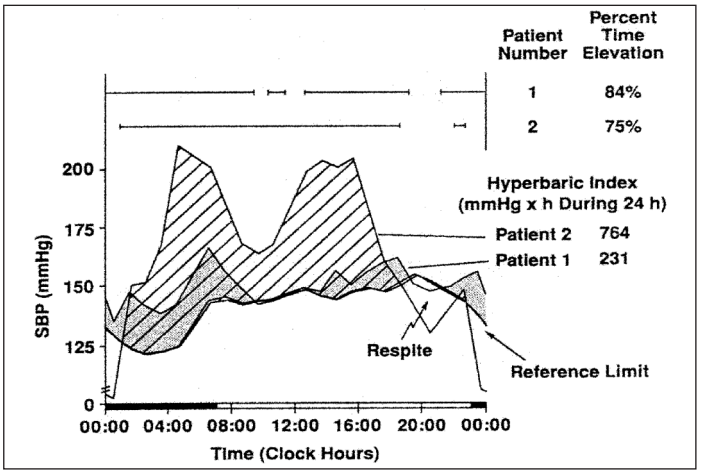

Figure 2: *The percentage time elevation of blood pressure above time-specified reference limits can be very similar between two patients but fail to convey the larger risk of patient #2 whose blood pressure reached much higher values than those of patient #1. The difference is better represented by the hyperbaric index, the area of excess delineated by the blood pressure record when it is above the upper limit of acceptability and the limit itself. © Halberg Chronobiology Center*

Since the availability of monitors for the automatic measurement of blood pressure, several protocols have been designed and used by us to assess the merits of timed-treatment (chronotherapy) of an

elevated blood pressure and other blood pressure abnormalities, the vascular variability disorders [17, 18]. Some of these study designs are described below to highlight their respective relative merits.

Blood pressure chronotherapy

Optimization of Prazosin in patients with idiopathic hypertension

The first optimization of an anti-hypertensive medication by timing designed by Franz Halberg in cooperation with Frederick C Bartter and Hans-Georg Güllner was published in 1979 [22, 23]. The study involved only 10 patients, but its design is impeccable. The anti-hypertensive treatment tested was the once-daily administration of prazosin, an α1-blocker which acts as an inverse agonist at alpha-1 adrenergic receptors. These receptors are found on vascular smooth muscle, where they are responsible for the vasoconstrictive action of norepinephrine. Prazosin had a plasma half-life of about 1.5 hours [23].

One important feature of the study design relates to the standardization of experimental conditions. The patients were admitted to a metabolic ward and fed constant diets; they were kept recumbent during the entire study to eliminate the effects of posture and physical activity on blood pressure. Since blood pressure can decrease by hospital admission itself, patients were monitored for 3 days before the start of intervention.

Another critical aspect of the study was the use of one of the first available automatic blood pressure monitors, the Roche "Arteriosonde", an analog device that needed calibration of both blood pressure and time, the measurements being recorded as dots on moving paper that had to be manually transcribed into numerical values and entered on punched cards for computer analysis. The drawback of small measurement errors introduced in the process was greatly overshadowed by the merit of obtaining data around the clock without the need to wake-up and disturb the study participants. Data were collected automatically every 30 minutes for the entire duration of the study.

Most importantly, the study followed a double-blind, placebo-controlled design. Every patient received one capsule, either active drug (1 mg prazosin) or placebo, every 4 hours for 7 days. Only one prazosin capsule was given every day. The time of prazosin administration was delayed by 4 hours every day.

Results showed a decrease in blood pressure by 5 to 12 mmHg (systolic) and 6 to 7 mmHg (diastolic), the greatest lowering observed when prazosin was administered at midnight. When given at 08:00 or at 12:00, prazosin was effective in lowering blood pressure for 24 hours, but when given at 04:00, it only lowered blood pressure for 13 hours. The results thus indicated that the effect and duration of prazosin's action depended not only on dosage, but also on the time of its administration [22, 23].

The only caveats are the fact that treatment at a given circadian stage lasted only one day (to keep the length of the study manageable), and that the study endpoints were limited to an effect on blood pressure itself without consideration for any modification of the circadian variation in blood pressure. These limitations are fully understandable since these data were among the first to be collected automatically around the clock. Very little, if any, information was available regarding the day-to-day variability in the circadian rhythm characteristics of blood pressure, or about vascular variability disorders and their relation to cardiovascular disease risk.

Comparison of presumed optimal chronobiologic timed treatment versus conventional dosing

Another chronotherapy protocol aimed at treating at the anticipated optimal circadian stage, based on the circadian blood pressure profile and the pharmacokinetics of the anti-hypertensive drug used [24, 25]. In this approach, results from the sphygmochron [20] are used as a guide to time treatment, which targets the time of peak drug action to the time of highest blood pressure excess.

This design from Dr. Rina Zaslavskaya was tested by her versus conventional treatment at the time, which consisted of dosing three times a day. The anti-hypertensive drugs tested were propranolol, clonidine, and α-methyldopa. Propranolol is a β-blocker. It appears in the blood after 30 minutes and has a maximum effect between 60 and 90 minutes when taken by mouth. Clonidine is classified as a centrally acting α_2-adrenergic agonist and imidazoline-receptor agonist that has been in clinical use for over 40 years. Effects of α-methyldopa start around 5 hours after administration and last about a day.

One feature of this design is that it is cost-effective since it consists of only two arms: the chronotherapy arm and the conventional (control) arm. One limitation of this design is that there is no verification that the selected treatment time is indeed the optimal time to treat. Since these trials also anti-date knowledge about vascular variability disorders, target endpoints included a lowering of the average blood pressure but not any effect of blood pressure variability or the circadian variation in blood pressure. Despite these shortcomings, results were very positive. As compared to once-traditional treatment three times a day, chronotherapy (applied 1.5 to 2 hours before the daily blood pressure peak, determined by around-the-clock measurements for the preceding 3 days) needed less drug to lower blood pressure more and faster, and was accompanied by fewer complications and less over-dosage [24, 25], Figure 3.

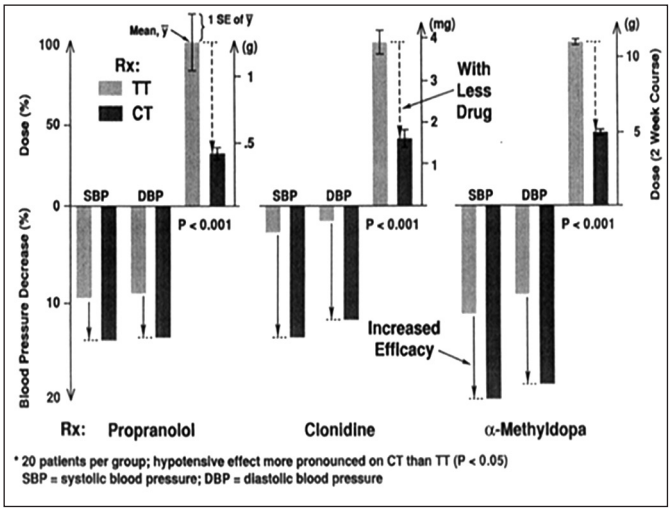

Figure 3: *A predicted best time, based on the pharmacokinetics of the drug and on the chronodiagnosis, was compared with treatment as usual (taken 3 times a day in equal doses). The chronobiologic timing was determined in such a way as to target the time of highest efficacy of the drug to match the time of highest blood pressure values predicted by model fitting. With all 3 drugs tested (propanolol, clonidine, and α-methyl-dopa), a larger reduction in the blood pressure MESOR was achieved with a smaller dose, resulting in fewer side effects (the latter not shown). Data of R Zaslavskaya. © Halberg Chronobiology Center*

Pilot N-of-6 studies

Before undertaking large clinical trials, it is often cost-effective to first proceed with smaller pilot studies aimed at determining the optimal circadian stage at which to administer a given treatment. Such pilot studies can be as small as N-of-6 studies, wherein 6 different circadian stages are tested, equally distributed along the 24 hours, or at least during the waking span from the time of awakening to bedtime. To yield reliable results, it is important that study participants be a random sample of the target population and that they be randomly assigned to the different treatment times.

One such N-of-6 pilot study tested effects of low-dose aspirin on blood coagulation and also on blood pressure [26]. As shown in Figure 4, the effect of low-dose (100 mg/day) aspirin on lipoperoxides in

platelet-rich plasma was highest when administered shortly after the time of awakening and lowest 9 and 12 hours after awakening. Similar results were found for an effect of low-dose aspirin on lymphocyte-β-adrenoceptors [26]. The circadian stage-dependent response of these two variables to low-dose aspirin, assessed by the fit of a 24-hour cosine curve to the treatment-versus-reference difference assigned to the time of treatment administration, was statistically significant in each case ($P<0.05$). Low-dose aspirin was also found to have a circadian stage-dependent effect on blood pressure. In this case, the blood pressure lowering was greatest in the afternoon and evening, Figure 5 [27].

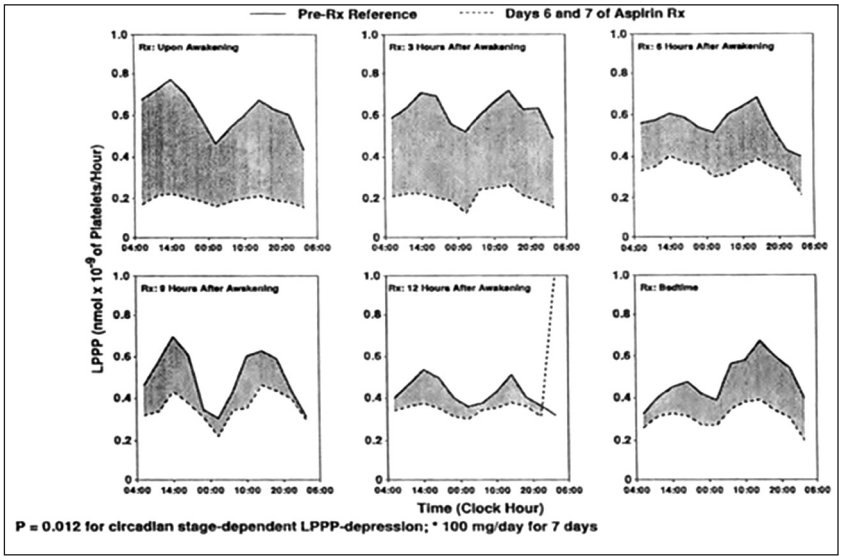

Figure 4: *The response of lipoperoxides is seen by plotting the 2-day around-the-clock profile obtained after 1-week treatment with low-dose aspirin for comparison with a similar profile obtained before treatment.*
© Halberg Chronobiology Center

Provided there is a marked effect of the tested intervention and that its effect has a marked circadian stage-dependent response, N-of-6 pilots can be very useful. In the case of low-dose aspirin, its effect on blood pressure assessed in this N-of-6 pilot was later confirmed based on a much larger population, yielding similar results [28]. One caveat, however, relates to the limited statistical power associated with the small number of study participants.

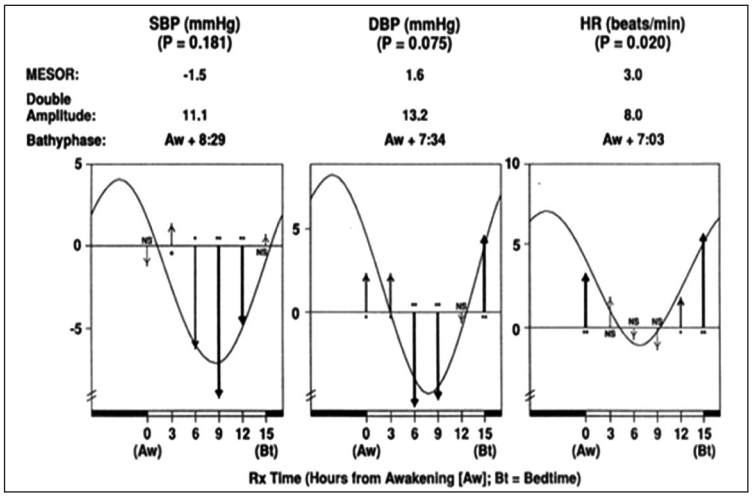

Figure 5: *The effect on blood pressure can differ from that on blood coagulation. Low-dose aspirin reduces the blood pressure MESOR most when it is administered in the afternoon, rather than shortly after awakening.*
© Halberg Chronobiology Center

Pilot N-of-1 studies

Ultimately, preference should be given to N-of-1 investigations since they underlie personalized optimization of treatment, recognizing that every patient is different. Individualized chronotherapy is made feasible by the availability of ambulatory blood pressure monitors for the automatic collection of around-the-clock measurements, preferably for longer than 24 hours, and of statistical methods for the analysis of data thus obtained.

Parameter tests [29] detect differences in the MESOR, amplitude, and acrophase tested either jointly or separately. It is thus possible to determine whether treatment at one circadian stage is preferable to treatment at a different circadian stage. This is illustrated in Figure 6 [30]: Diltiazem hydrochloride (240 mg) taken daily around 04:30 during an interruption of sleep, as compared to after awakening around 08:30, by a 75-year old hypertensive man was associated with both a lowering of the MESOR of systolic blood pressure from 147.7 ± 2.1 to 141.7 ± 1.0 mmHg (P=0.017) and a reduction of the double circadian amplitude from 34.2 ± 6.0 to 19.6 ± 3.0 mmHg (P=0.039). The reduction in circadian amplitude is thought to have been beneficial since before switching the treatment time 4 hours earlier, the circadian amplitude was above the upper limit of acceptability.

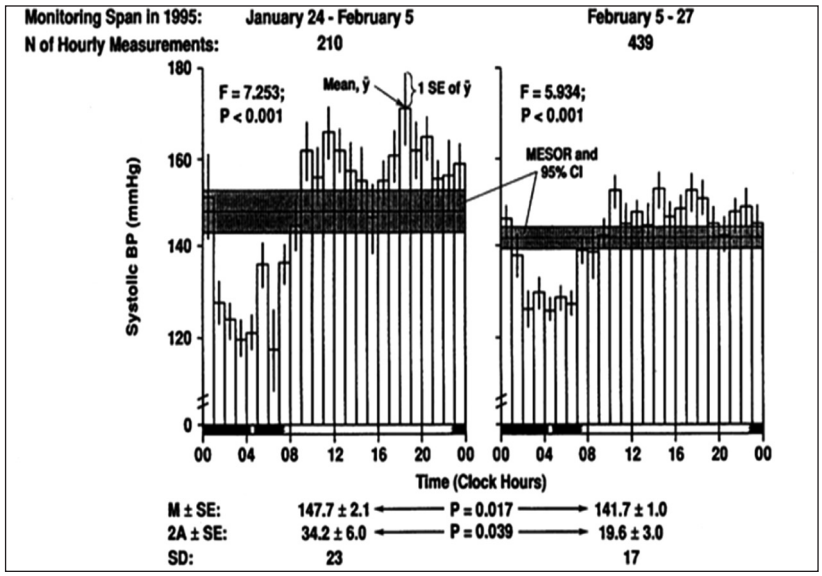

Figure 6: *The same dose of the same anti-hypertensive medication (Diltiazem HCl) can lower the blood pressure MESOR to a larger extent, and it can also reduce an excessive circadian amplitude of blood pressure when given at one rather than at another circadian stage. The difference in effect can be assessed for the individual patient by means of parameter tests. © Halberg Chronobiology Center*

The self-starting cumulative sum (CUSUM) control chart [31] can be used to assess the effectiveness of a given intervention for the individual patient. In this approach, a break-out of one of the two (upward/downward) CUSUM curves outside the decision interval (shaded band) indicates that a statistically significant change (increase/decrease) in the endpoint examined took place. Following the CUSUM curve backwards to the time when it first deviates from zero provides an estimate of when the change started to take effect. As opposed to applications in industry, in medicine the start of treatment is known (recorded) and if this time coincides with the time when the CUSUM line first departs from zero, then a causal relation may be assumed [32]. An example is provided in Figure 7 (top). The MESOR of systolic blood pressure of a man newly diagnosed with hypertension decreases, starting almost immediately once anti-hypertensive treatment is started, but the efficacy of the treatment is only detected after a couple of weeks [33]. Figure 7 (bottom) indicates that when anti-hypertensive medication is taken

daily in the evening, the circadian amplitude of systolic blood pressure is increased. Since this patient already had an excessive circadian amplitude of blood pressure, evening dosing should be avoided.

Methodologic considerations for the design of clinical trials: transverse versus longitudinal design

Studies on groups of patients are best designed to include more than two test times. In other words, more than two circadian stages at which to administer the anti-hypertensive medication need to be considered. Depending on the response rhythm to the given treatment, selecting two treatment times about 12 hours apart, such as morning and evening, may correspond to the midline crossing of the response rhythm. If so, no difference will be detected, even if benefit could be derived from treating at a different circadian stage [34, 35].

It is also recommended to measure blood pressure around the clock so that the circadian variation can be assessed. Indeed, treatment can also affect the amplitude and/or acrophase of the circadian rhythm in blood pressure, in addition to lowering the MESOR. If this is the case, measuring blood pressure always at the same clock hour may yield inaccurate results and even opposite results when measurements are taken at another time [36]. Some, but not all anti-hypertensive medications affect the circadian amplitude of blood pressure [37, 38].

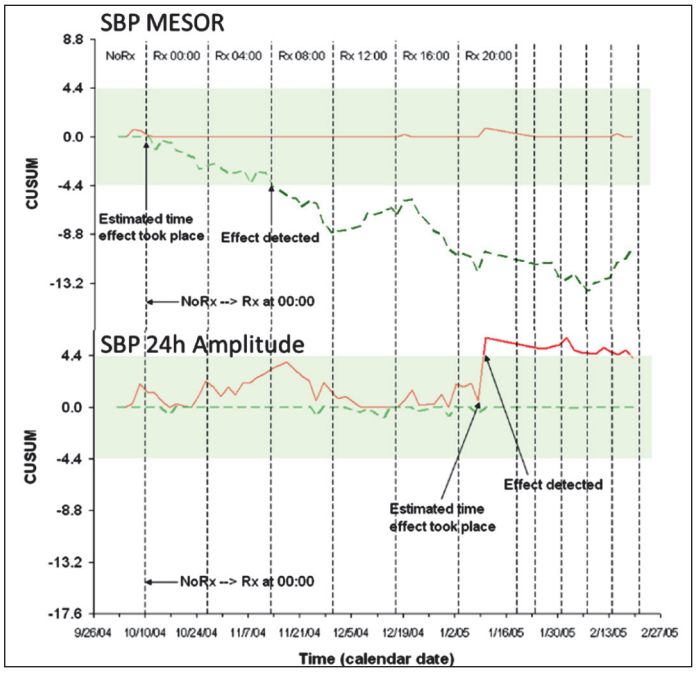

Figure 7: *The same dose of Diovan HTC (80/12.5) was taken at the same circadian stage for 17 days before the treatment time was advanced by 3-4 hours. After all 6 circadian stages had been tested, the protocol was repeated with shorter spans on each treatment time. As seen from the self-staring CUSUM, the initiation of treatment was effective in bringing about a statistically significant decrease in the MESOR of systolic blood pressure, the effect being detected after about one month. When treatment was taken in the evening, it was associated with a statistically significant increase in the circadian amplitude of blood pressure. © Halberg Chronobiology Center*

One example of a small clinical trial using six different test times between 08:00 and 18:00 enrolled 24 presumably normotensive individuals, who were randomly assigned to one of six times to undergo periodontal surgery [13]. Blood pressure was measured around the clock by ambulatory monitoring on three occasions, bracketing dental visits. Periodontal surgery was performed on the last visit. Whereas the blood pressure of patients undergoing periodontal surgery in the morning increased in response to the intervention, the blood pressure of patients similarly treated in the afternoon decreased. The

blood pressure response to periodontal surgery was shown to be circadian stage-dependent by one-way ANOVA and by cosinor, a 24-hour cosine curve being fitted to the difference in blood pressure associated with the dental procedure ($P<0.05$) [13].

In the above study, the design was transversal, since different patients were assigned to different circadian stages at which periodontal surgery was to be performed. The same recommendations of considering more than two treatment times and to automatically measure blood pressure around the clock to assess the response to treatment also apply to longitudinal designs. In longitudinal studies, patients serve as their own control, and each patient in such clinical trials can also be considered as different N-of-1 cases. Doing so allows the personalized optimization of treatment while still deriving average results for the target population.

Clinical trials are usually based on a transversal design. While only average results for the population can be derived from this approach, one advantage is that patients can be kept in their respective arms of the study for as long as desired. When followed-up over a sufficiently long time for adverse events to have occurred, the data are amenable to logistic regression estimating any benefit to be derived not just in terms of the marker variable (usually blood pressure lowering) but also in terms of actual target organ damage.

Examples of chronotherapy trials based on a longitudinal design

Clinical trials based on a longitudinal design have thus far been limited to assessing benefit derived in terms of changes in the marker variable(s) (blood pressure and heart rate). Outcome studies focused on benefits to be derived in terms of the incidence of actual adverse cardiovascular events will need to first determine for each patient the optimal treatment regimen, then compare the occurrence of adverse events between patients thus treated chronobiologically versus similar patients treated conventionally, without consideration of timing, since the optimal treatment time will differ among patients.

In longitudinal designs, the optimal duration of treatment on any administration time has not yet been determined. It should be long enough for its full effect to have taken place, but not too long to avoid interference from other sources, such as the modulation of the circadian blood pressure rhythm by the circannual variation.

In one trial, the time of administration of Micardis (Telmisartan, an angiotensin II receptor antagonist), with or without low-dose aspirin, was changed every day [39]. In this cross-over, double-blind, randomized study, 20 MESOR-hypertensive patients were recruited. The study consisted of three stages (placebo, Micardis, and Micardis with low-dose aspirin), each lasting 7 days. The treatment was administered each day at a different circadian stage, 3 hours apart, from the time of awakening to bedtime. In addition to the lowering of blood pressure, Micardis was associated with a reduction of the circadian amplitude of blood pressure, the effect being more pronounced when low-dose aspirin was added to Micardis. While Micardis was most effective in decreasing blood pressure when taken 6 to 9 hours after awakening, it was concluded that monitoring over spans longer than one day on a given regimen was required to reliably estimate the optimal treatment time [39].

In another trial, Hyzaar (Losartan/hydrochloride, an angiotensin II receptor antagonist combined with a diuretic) was administered for at least one month at a given circadian stage to each of 30 hypertensive patients [40]. The time of treatment administration was changed during consecutive spans to cover six treatment times from awakening to bedtime at approximately 3-hour intervals. At the end of each span during which Hyzaar was taken at a given circadian stage, each patient contributed a 7-day record of around-the-clock ambulatory blood pressure monitoring [40]. Overall, a larger reduction of the MESOR of diastolic blood pressure was achieved when Hyzaar was taken in the

early morning for more patients, while treatment upon awakening was the best choice for most patients to reduce the circadian amplitude of blood pressure the most. Importantly, the optimal treatment time differed considerably among patients [40].

Discussion and Conclusion

Since abnormal blood pressure variability also relates to an increased cardiovascular disease risk, chronotherapy of blood pressure should assess effects on all circadian characteristics, and not just on the 24-hour average (MESOR). As noted above, not all anti-hypertensive drugs have an effect on the circadian amplitude [37, 38]. Restoring an acceptable circadian blood pressure rhythm can be more important than lowering the blood pressure MESOR to a larger extent. Evidence stems from a cross-over, double-blind, randomized study comparing the effect of two calcium channel blockers: benidipine given once a day in the morning, and nifedipine given twice a day, in the morning and evening [41]. Whereas nifedipine lowered blood pressure to a larger extent than benidipine, only benidipine also reduced the circadian amplitude of blood pressure. This effect on the circadian amplitude of blood pressure is thought to account for the considerably lower incidence of stroke and overall cardiovascular events in a large trial of benidipine [42] compared to outcomes from two other large clinical trials of nifedipine (the STONE and Syst-China trials) [43, 44]. These trials were all performed in Asia where an excessive circadian amplitude of blood pressure may be more prevalent and was associated with a large increase in adverse outcomes [18].

In the experimental laboratory, treating at the optimal circadian stage was documented to prolong survival [45], Figure 8. Chronotherapy of Temocapril, an angiotensin-converting enzyme (ACE) blocker, led to more than the doubling of the survival time of salt-loaded, spontaneously hypertensive stroke-prone (SHR-SP) rats. Animals treated daily early during the light (rest) span lived longer than animals treated early during the dark (active) span.

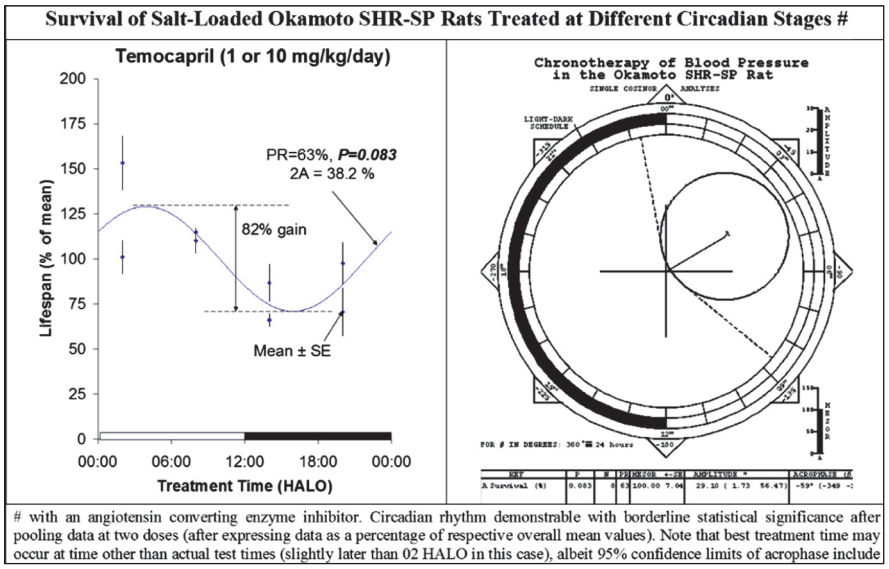

Figure 8: *The efficacy of anti-hypertensive drugs can also be optimized by timing, as shown here in terms of the effect of Temocapril on the lifespan of stroke-prone Okamoto rats. Data of A Fujimura. © Halberg Chronobiology Center*

In the clinic, results from the Hyzaar trial show that individualized chronotherapy is estimated to help more than half the patients in need of anti-hypertensive medication, when treatment is targeted

to restore an acceptable circadian variation of blood pressure and heart rate. Intuitively, it makes sense that the best time to treat will differ for a patient with an excessive circadian amplitude of blood pressure (CHAT, short for Circadian Hyper-Amplitude-Tension) who has the largest blood pressure excess in the afternoon than for a patient who has a reversed circadian variation of blood pressure (ecphasia) who has the largest blood pressure excess at night. Ecphasia can occur in patients with non-insulin-dependent diabetes mellitus complicated by autonomic nervous dysfunction [46].

Since patients can present with widely different circadian patterns of blood pressure and heart rate as illustrated in a series of case reports [16], and thus with different combinations of vascular variability disorders, it makes sense to adjust the timing of treatment (chronotherapy) to the chronodiagnosis. This concept has been referred to as chronotheranostics [36].

In summary, in order to obtain a reliable chronodiagnosis, blood pressure needs to be measured around the clock for longer than 24 hours, preferably for 7 days or longer. Chronotherapy should aim at restoring acceptable circadian rhythms of blood pressure in addition to lowering blood pressure. Tailoring chronotherapy to the chronodiagnosis implies personalization of treatment timing. Chronotherapeutic designs should include treatment at 5 or 6 different circadian stages equally distributed over the active span (from awakening to bedtime), if not over the full 24 hours.

The availability of monitors to automatically collect blood pressure data around the clock and of methods for their analysis now renders it feasible to test more than two treatment times -- the conventional morning versus evening dosing -- in order to truly implement a personalized optimization of treatment by timing. Further work is needed (1) to determine the duration of treatment at a given circadian stage during the optimization stage, (2) to proceed with outcome studies comparing the incidence of adverse cardiovascular events on personalized chronotherapy versus conventional treatment, and (3) to determine modalities for the continued monitoring at intervals to ascertain that the prescribed treatment regimen remains effective in maintaining acceptable circadian variation in blood pressure and heart rate.

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Chronobiology, Mitochondria, and Cardiovascular Disease

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Abstract

Halberg defined chronobiology as the science objectively quantifying and investigating mechanisms of biologic time structure, including rhythmic manifestations of life. The term is derived from: Chronos meaning time, bios (life), and logos (science). Biological rhythms are essential to all living organisms. Covering a wide range of frequencies, the circadian (about 24-hour) rhythm is manifested in both health and disease. Circadian rhythms in all living organisms can be influenced or synchronized by environmental factors, such as the lighting regimen and feeding schedule, but their partly endogenous nature is now well documented at the molecular level. The suprachiasmatic nuclei (SCN) located in the hypothalamus are considered by many to be the master clock that orchestrates the organism's biological rhythms, which are then carried out in almost every cell in the body by different parts of the cell. The mitochondria consist of a double-membraned organelle where cellular metabolism takes place in a rhythmic pattern. Most cells in the body need mitochondria for energy production. Some cells that need lots of energy include those in muscle, kidney, and primarily heart. Circadian rhythm parameters are useful gauges of health and disease risk. Alterations in circadian rhythm parameters (MESOR, amplitude, and acrophase) related to cardiovascular diseases indicate mitochondrial dysfunction. In order to evaluate the role of mitochondria in the heart and cardiovascular diseases, this review looks into their mechanism and function, and reviews how chronobiology may help investigations of the role played by mitochondria in cardiovascular diseases.

Keywords

ATP, Cardiovascular Disease, Cellular Energy, Chronobiology, Circadian Rhythm, Mitochondria

Chronobiology

Introduction

The knowledge of rhythms dates back to the very beginning of life on this planet. All living matter and the evolving organisms were exposed to the earth‘s revolution around the sun with its periodicity of day and night, light and darkness, with the periodic changes in the length of the daily light and dark span in relation to the climatic changes of the seasons. In addition, some aquatic life forms were exposed to the periodic input provided by the cycles of the moon with its influence on ocean tides (Touitou & Haus, 1992). It was a necessity for all life forms (early in the beginning and even later) to adapt to the periodically changing environment on our planet. The related periodic functions, originally in response to environmental stimuli, may have impressed themselves on the genetic makeup of living matter. Periodic variations, many but not all of which follow the frequencies of the periodic environmental input, are found in the most primitive and ancient forms of life presently available for study. Many other periodic functions, however, have no known environmental counterpart (Touitou & Haus, 1992).

Biological rhythms are inherent to most if not all living organisms in one form or another and are noted at all levels of biological organization, from intracellular processes, tissues, organs and organ systems to the individual, populations, and the biosphere (Halberg, 1969; Halberg et al., 2001b). They also span a broad frequency range, periods varying from milliseconds (activity of single neurons), seconds (heart beat and respiration), hours (about 90-minute basic rest-activity cycle), to days (circadian), weeks (circaseptan), and months (circatrigintan) to years (circannual) and even decades (Halberg et al., 2001b). Probably the most widely known and understood is the circadian rhythm which plays a special role ever since its partly endogenous nature was placed on a solid molecular basis and core clock genes were shown to be implicated in major disease conditions (Cornélissen & Otsuka, 2017).

Many chronobiologists have investigated circadian and other rhythms in both health and disease (Halberg, 1969; Halberg, et al., 2012; Haus et al., 1988, 2001; Lewy et al., 2007; Nicolau et al., 1989, Singh et al., 2002; Sothern et al., 2009). Circadian rhythm parameters can be estimated by the least squares fit of a 24-hour cosine curve with or without the addition of harmonic terms. They include the MESOR (Midline Estimating Statistic Of Rhythm, the value midway between the highest and the lowest values of the cosine function best fitting the data), the amplitude (half the predictable extent of change within a cycle), and the acrophase (a measure of the timing of overall high values recurring in each cycle), Figure 1. The period (τ), the duration of one complete cycle, reported in time units, is often assumed to be 24 hours under 24-hour synchronized conditions. The MESOR equals the arithmetic mean when data are equidistant and cover an integer number of cycles. The MESOR and amplitude are expressed in the same units as the original data (i.e., blood pressure in mmHg), and the acrophase is expressed in relation to the reference time as negative degrees (with -360° = period; 0° = reference time).

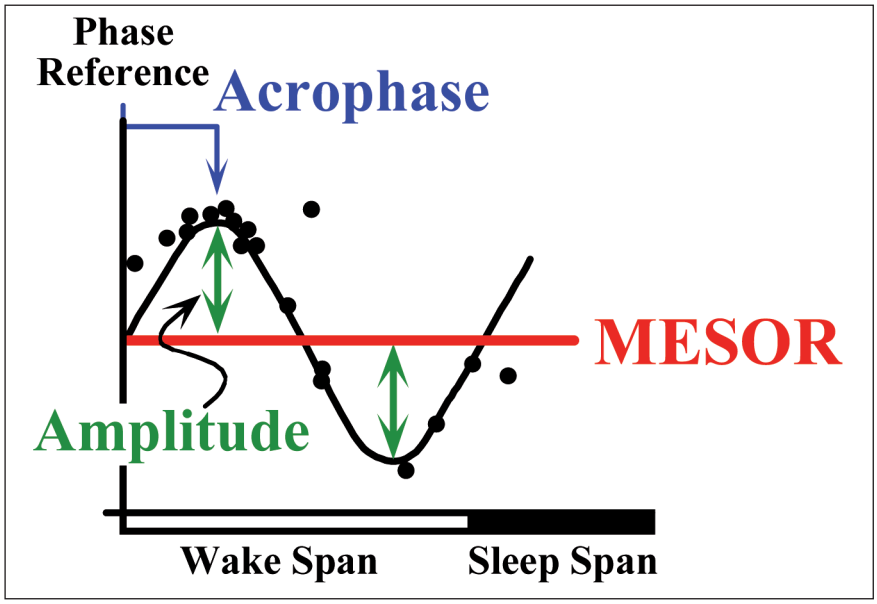

Figure 1: *Example of a cosine function for a complete 24-hour cycle, showing the MESOR, amplitude, and acrophase of the best-fitting cosine curve. © Halberg Chronobiology Center*

History of Chronobiology

Prehistoric man, the hunter and gatherer of food for the family, was familiar with the concept of time and the environmental periodicities related to its passage. They may not have understood biological

rhythms, but they knew that there were times when they could hunt and gather food depending on the time of the day and/or the changing of the seasons.

There are many references in the literature referring to periodicities as a function of time. In the Bible the importance of temporal factors was recognized as stated in Ecclesiastes: "To everything there is a season and a time to every purpose under the Heaven: a time to be born and a time to die; a time to plant and a time to harvest." In Genesis, the first task of God was to create light and then the alternation of light and darkness. Also the 7-day cycle of activity and rest is part of the story of creation as presented in the Old Testament; the 6 days of work were followed by a day of rest. It is believed that the Egyptian calendar was invented around 4200 BC (Touitou & Haus, 1992).

Ancient physicians already realized the presence of rhythms in certain aspects of disease, notably rhythms of about 7 days, when they noticed that certain symptoms would either ease or worsen. Greek physicians and naturalists (Aristotle, Hippocrates, Diocles) observed that some symptoms recurred predictably according to patterns of about 7 days such as intermittent fevers. The life cycle of the malarial parasite (Sanchez de la Peña et al., 1984) could now account for some of these observations. Aristotle believed that the moon influenced reproductive functions and disorders that affected women. He also believed the heart to be the organ that controlled sleep and awake times, contrary to Galen, who felt that it was the brain. Hippocrates described that crises in diseases occurred at regular intervals and that these intervals may be related to celestial body movements. Diocles figured the number 7 played an important role in the periodicities of health and disease (Touitou & Haus, 1992).

Aschoff (1974) suggested that the history of rhythm research began in 650 BC, when the Greek poet Archilochus of Paros wrote "Recognize which rhythms govern man". As noted by Halberg et al. (2001a), a later fragment by Archilochus refers to the solar eclipse of 6 April 647 BC, which authenticates the fragment on rhythm as dating from the seventh century BC, and identifies Archilochus as a lyric link to both the study of rhythms and to that of the Sun.

In ancient days it was generally accepted that any cyclic changes in an organism represented exclusively the effects of cyclic changes in environmental factors. Some of the first observations that led to the recognition of the endogenous nature of certain periodicities were made in 1729 when the French astronomer Jean-Jacques d'Ortous de Mairan reported that the daily changes in the position of the appendages of the heliotrope plant, Mimosa pudica, whose inflorescences turn their rows of flowers to the sun, persisted in continuous darkness (Robertson McClung, 2006). This observation was followed in 1745 by the designation of a „flower clock" by Carl Linnaeus (Carl von Linné), who showed that at certain sun-related clock hours the flowers of some plant species are open while those of others are closed (Touitou & Haus, 1992). When in 1832 Augustin Pyramus de Candolle, a Swiss botanist, finally measured what de Mairan observed, he found that the leaf movement of Mimosa pudica not only persisted in complete darkness, its period of 22-23 hours also free-ran from the environmental 24-hour cycle. De Candolle also showed that the leaf movements could be reversed by inverting the light/dark schedule (Robertson McClung, 2006). These findings, probably not completely understood by botanists at the time, were likely the first description of the partly endogenous nature of the about 24-hour rhythm that can be synchronized by the lighting regimen.

Many more discoveries were made since the 1800s. Julien-Joseph Virey in 1814 wrote his doctorate thesis in Medicine on diurnal rhythms in health and disease in humans, were he emphasized the importance of timed therapy (Touitou & Haus, 1992). Balfour (1815) tried to predict fevers according to the lunar cycle and according to the timing of previous attacks and suggested that treatment should be timed according to the expected occurrence of the next attack of the disorder (Touitou & Haus, 1992). In humans, Thomas Laycock proposed in 1842 that periodicity originated from within the system („isoteric origin") or was caused by periodic factors acting from without („exoteric origin") or

by a combination of both („endoexoteric“) (Lavie, 1992). Edward Smith (1861) wrote a book “Health and Disease: as Influenced by the Daily, Seasonal, and other Cyclical Changes in the Human System”, where he reports on rhythms in health and disease, even stating in his Preface: “…that no work of modern date exists in which the cyclical changes proceeding in the human system are described, or in which even the influence of season is cited at any length in reference to the causation and treatment of disease” (Smith, 1861). He reported a higher toxicity of ethanol in the morning and stressed that drug effects are cycle-stage dependent. Smith (1861) also reported a circadian periodicity of time of death: „death occurs much more frequently from 1 to 5 a.m. (Lavie, 1992).

In the 1900s, the field exploded with many new investigators with many new findings and studies taking place. The 1960 symposium at Cold Spring Harbor Laboratory laid the groundwork for the field of Chronobiology (Cold Spring Harbor Symposium, 1960). One physician who had started to study changes as a function of time was the young Dr. Franz Halberg, who while counting mouse eosinophils found that the counts depended on when the eosinophils were harvested in relation to the light/dark regimen (Halberg & Visscher, 1950). Franz Halberg also deserves credit for recognizing the critical importance of circadian rhythms in view of their partly endogenous nature and the difference they make between life and death. It was not until around 1959 that the word circadian started to replace 24-hour periodicity. Franz Halberg wrote in 1959: “in discussions with Professor William McDonald (and others) of the Department of Classics at the University of Minnesota, the term ‘circadian’ was derived from ‘circa’ (about) and ‘dies’ (day); it may serve to imply that certain physiologic periods are close to 24 hours, if not of exactly that length” (Halberg, 1959). By collecting a critical mass of data documenting the ubiquity of circadian rhythms, by developing statistical methods for their analysis and quantitative assessment, and by meticulously presenting a host of practical clinical applications, Halberg laid the foundation for the new discipline of chronobiology (Cornélissen et al., 1989). The field then started to explode, with many more researchers who contributed greatly to the field (for review, see Touitou & Haus, 1992; Lemmer, 2009; Otsuka et al, 2016).

Much interest in circadian rhythms in recent years stems in part from the discovery of clock genes that provided a molecular mechanism for their manifestation (Konopka & Benzer, 1971). While clock genes reside in almost every cell, those in the suprachiasmatic nuclei (SCN) are thought by many to be the most important since they may orchestrate the entire circadian system. The SCN is a tiny region of the brain in the hypothalamus, situated directly above the optic chiasm. Apart from the core Clock genes (Clock, Bmal1, Cry and Per), other genes continue to be discovered that participate in the coordination of circadian rhythms. This is now an entire field of research since clock genes have also been found to underlie a host of disease conditions (Mazzoccoli et al., 2012).

Chronobiology in Health & Disease

Even before attention was given to clock genes in relation to health and disease, circadian rhythm characteristics served as markers of health in screening for disease and pre-disease. Time-specified reference values in health from womb to tomb have been made available for blood pressure (Cornélissen et al, 1992, 1993; Halberg et al., 1992, 1993), endpoints of heart rate variability (Otsuka et al., 1999), hormones (Halberg et al., 1981; Haus et al., 1988), and biochemical variables (Haus et al., 1988).

Deviations from these chronobiologic norms have been shown to associate with disease conditions (neurological, metabolic, endocrine and cardiovascular diseases) as well as with aging. Of interest herein is the relationship between biological rhythms of different frequencies in cardiovascular disease and mitochondrial function and/or dysfunction.

Mitochondria

Introduction

Mitochondria are double-membraned organelles found in the cells of all eukaryotic organisms, considered to be the power generators of the cell, converting oxygen and nutrients into adenosine triphosphate (ATP). Siekevitz, in 1957, called the mitochondria the "powerhouses of the eukaryotic cells".

Besides supplying energy to the cell, mitochondria are involved in other tasks (McBride et al., 2006): 1) signaling - part of any communication process that governs basic activities of cells and coordinates all cell actions; 2) cellular differentiation - process where a cell changes from one cell type to another; and 3) cell death or apoptosis - process of programmed cell death that occurs in multicellular organisms. Mitochondria also help in maintaining control of: 1) the cell cycle - series of events that take place in a cell leading to its division and duplication of its DNA to produce two daughter cells; and 2) cell growth - biological cell development and cell division (reproduction).

Much was known about the mitochondrion as an organelle before it was determined that it also has its part/assignment in the biologic rhythms of the organism. The mitochondrion is the organelle where the final stages of cellular respiration occurs: i.e., the Kreb's cycle and the electron transport chain. The cells in the body that use a lot of energy have the highest numbers of mitochondria in them. In particular, muscle cells in the heart need lots of energy all of the time. Whereas leg muscles can rest, heart muscles are always working.

Mitochondria are the chief producers of ATP, which is the transporter of chemical energy for the cell, to be used in metabolism. ATP is a small molecule nucleotide used in cells as a coenzyme and a nucleotide used in the formation of DNA and RNA. It is often referred to as the „molecular unit of currency" of intracellular energy transfer that powers the cell's metabolic activities (Knowles, 1980). The inner membrane of the mitochondrion is highly folded into cristae, which house the megadalton complexes of the electron transport chain and ATP synthase involved in the basic rates of cellular metabolism, Figure 2.

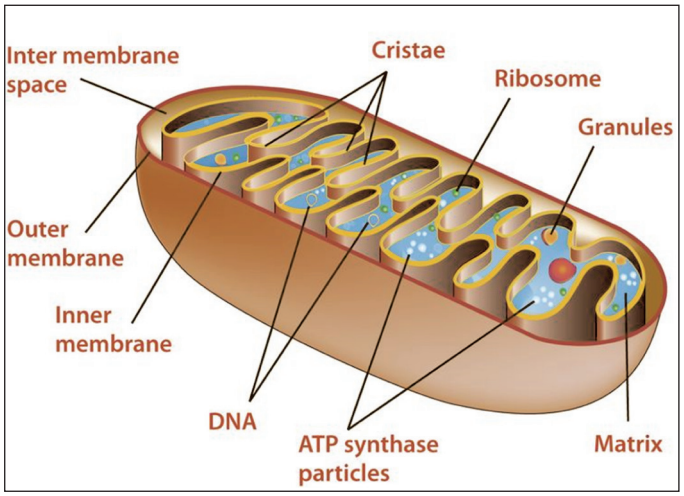

Figure 2: *Structure of mitochondrion showing the outer porous membrane and the inner impermeable membrane with cristae where ATP is produced (reproduced from Wikipedia)*

Chronobiology of Mitochondria

Circadian variations have been found in mitochondrial oxidative phosphorylation and coenzyme Q10 (CoQ10) (Gvozdjáková et al., 2014). Cardiac function relies on a time-varying supply of oxidative energy during the mitochondrial oxidative phosphorylation produced by mitochondrial respiration (Kohsaka et al., 2014). CoQ10 is a fat-soluble substance, also in the mitochondria, that participates in the cellular respiration process, generating energy in the form of ATP (Dutton et al., 2000). Both circadian and circaseptan (about-weekly) variations in ATP have been documented by Ulmer et al. (2001), Figure 3. CoQ10 is an antioxidant that is needed for basic cell function. CoQ10 concentrations decrease with age and may be low in people with hypertension and other heart conditions, along with other diseases. While continuously monitoring her blood pressure around the clock, one healthy woman took CoQ10 daily, changing the timing of supplementation every 7 days, starting shortly after awakening, then delaying administration time by about 3.5 hours every week until it was taken around bedtime. Treatment time was then advanced weekly by about 3.5 hours. Figure 4 shows the circadian stage-dependent effect of CoQ10 on the 24-hour amplitude of systolic blood pressure (SBP). When CoQ10 was taken in the morning, the circadian amplitude of SBP was much larger than when the same dose of CoQ10 was taken in the late evening. In this subject, evening dosing was desirable since her circadian amplitude of SBP was excessive.

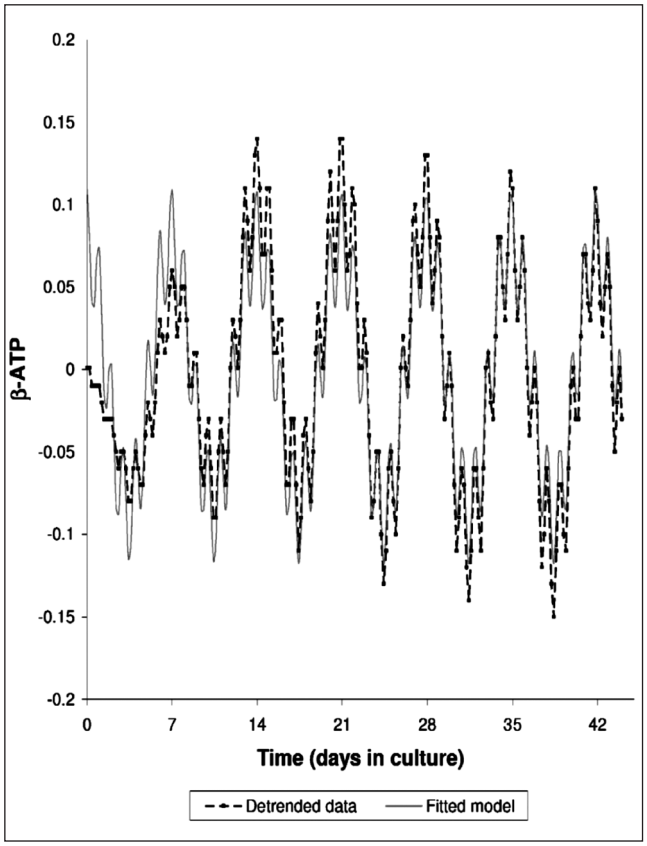

Figure 3: *Time dependence of beta-ATP in L1210 leukemia cells (detrended data). Both the circadian and the circaseptan components characterizing beta-ATP are statistically significant. Note that the 7-day amplitude is much larger than the 24-hour amplitude. © Halberg Chronobiology Center*

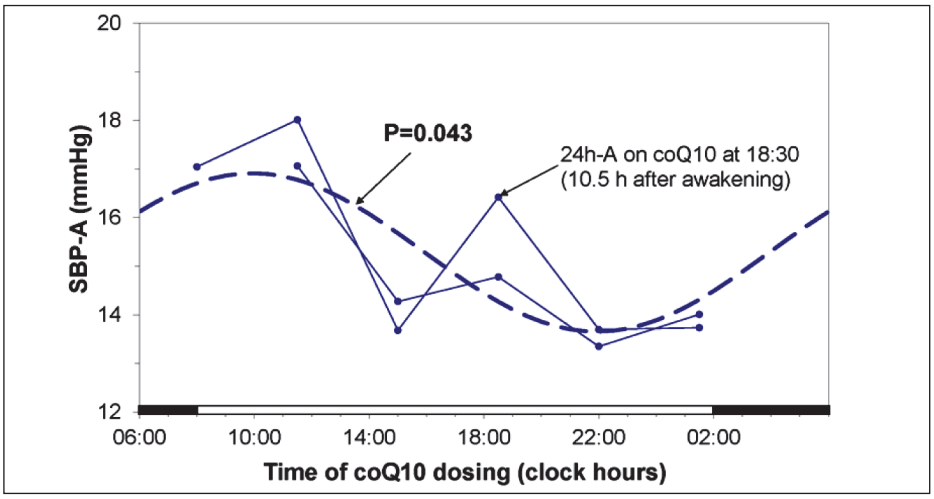

Figure 4: *Circadian stage-dependent effect of CoQ10 supplementation on the 24-hour amplitude of SBP of a clinically healthy woman. © Halberg Chronobiology Center*

Mitochondrial Function

McBride et al. (2006) suggested that the broader question remains regarding the underlying purpose of mitochondrial dynamics and the translation of these morphological transitions into altered functional output. One hypothesis is that mitochondrial respiration and metabolism may be spatially and temporally coordinated by the architecture and positioning of the organelle. Recent evidence supports and expands this idea by demonstrating that mitochondria are an integral part of multiple cell signaling cascades. Interestingly, proteins such as GTPases, kinases and phosphatases are involved in bi-directional communication between the mitochondrial reticulum and the rest of the cell. These proteins link mitochondrial function and dynamics to the coordination of metabolism, cell-cycle control development, antiviral responses and cell death (McBride et al., 2006).

History of Mitochondria

The earliest records of intracellular structures that most probably represent mitochondria date back to the 1840s by Henle (Ernster & Schatz, 1981). In 1890, Altman described these structures as occurring everywhere and called them "bioblasts". He describes the "bioblasts" as "elementary organisms living inside cells and carrying out vital functions" (Ernster & Schatz, 1981). In 1898, the term "mitochondrion" was introduced by Carl Benda, from the Greek "mitos" meaning thread and "chondros" meaning granule (Benda, 1898). In 1912, Benjamin F. Kingsbury was the first to relate the mitochondrion with cell respiration, but his results were almost exclusively based on morphological observations. In 1913, Otto Henrich Warburg took particles, which he called "grana" from extracts of guinea-pig liver and linked them to respiration. Finally in 1925, David Keilin discovered cytochromes and the respiratory chain was described. Some mitochondrial structure, i.e., the outer membrane, could be seen under the light microscope, which was confirmed in 1945 by Claude and Fullam by electron micrographs (Ernster & Schatz, 1981). It was not until the early 1950s that Palade (1952, 1953) and Sjöstrand (1953a,b) published the first high-resolution electron micrographs of mitochondria. Palade's micrographs showed that the mitochondrial membrane is folded to form ridges which he called "cristae mitochondriales" (Palade, 1952). Sjöstrand's micrographs showed the double membranes inside the mitochondrion that had divisions or septae in the inner chamber of the cell (Sjöstrand, 1953a,b). For a detailed history of mitochondria, see Ernst and Schatz (1981).

As reviewed elsewhere (Cornélissen et al., in press), chronobiological aspects of mitochondria were studied at least since the 1960s. In the 1970s, circadian variations in mitochondria were investigated by Heinz von Mayersbach (1983), Karl Philippens (1968, 1970, 1971, 1973) and their team, as they used succinate dehydrogenase (SDH) as a marker enzyme to visualize mitochondria histochemically. Biochemical studies figuring the mitochondria as the "powerhouse of the cell", combined with the unique evolutionary origin of the mitochondria, led the way to decades of research focusing on the organelle as an essential, yet independent, functional component of the cell. Recently, however, our conceptual view of this isolated organelle has been profoundly altered with the discovery that mitochondria function within an integrated reticulum that is continually remodeled by both fusion and fission events. The identification of a number of proteins that coordinate these activities is beginning to provide mechanistic details of mitochondrial membrane remodeling.

Mitochondria in the Heart

Mitochondrial respiration takes place in the inner mitochondrial membrane in heart cells through a series of metabolic reactions using oxygen and nutrients in the cell to produce ATP, the source of energy in the cells (Gvozdjáková et al., 2014). About 90% of the ATP in the heart is produced from these oxidation-reduction reactions in the mitochondria, with the mitochondria consisting of 20% to 40% of the cardiomyocyte volume (Gvozdjáková et al., 2014). Gvozdjáková et al. (2014) showed in isolated mitochondria of the heart muscle of rats that ATP production in the mitochondrial respiratory chain in heart muscle and CoQ10 concentrations vary along the 24-hour scale (Gvozdjáková et al., 2014). Changes in OXPHOS and CoQ10 myocardial mitochondria may be involved in the pathophysiology of the heart muscle. A low CoQ10 concentration and an impaired OXPHOS in heart mitochondria are considered to be a molecular basis for heart failure and can trigger an acute myocardial infarction, cardiac arrest or stroke, all of which can end in sudden death (Gvozdjáková, 2008).

Chest pain associated with acute myocardial infarction is more prevalent in the second quarter of the day (Singh et al., 2003). In addition, it has been known for some time that the onset of heart failure, myocardial infarction, and sudden death is greatest in the early hours of the morning. There are clinical implications of the circadian rhythms of hemostatic and related mechanisms that happen during the morning hours. There is a morning rise in blood viscosity, vasoconstriction, vascular response to norepinephrine, blood pressure, platelet activity, and blood coagulability/fibrin formation. Parallel to these increases is a decrease in fibrinolytic activity. The combination of these events leads to fibrin accumulation and a risk of thrombosis with cardiovascular and cerebrovascular accidents and embolisms. In a group of patients, we were able to look at the circadian and circaseptan timing of cardiac mortality and the incidence of primary intracerebral hemorrhage, Figure 5 (Nicolau et al., 1991).

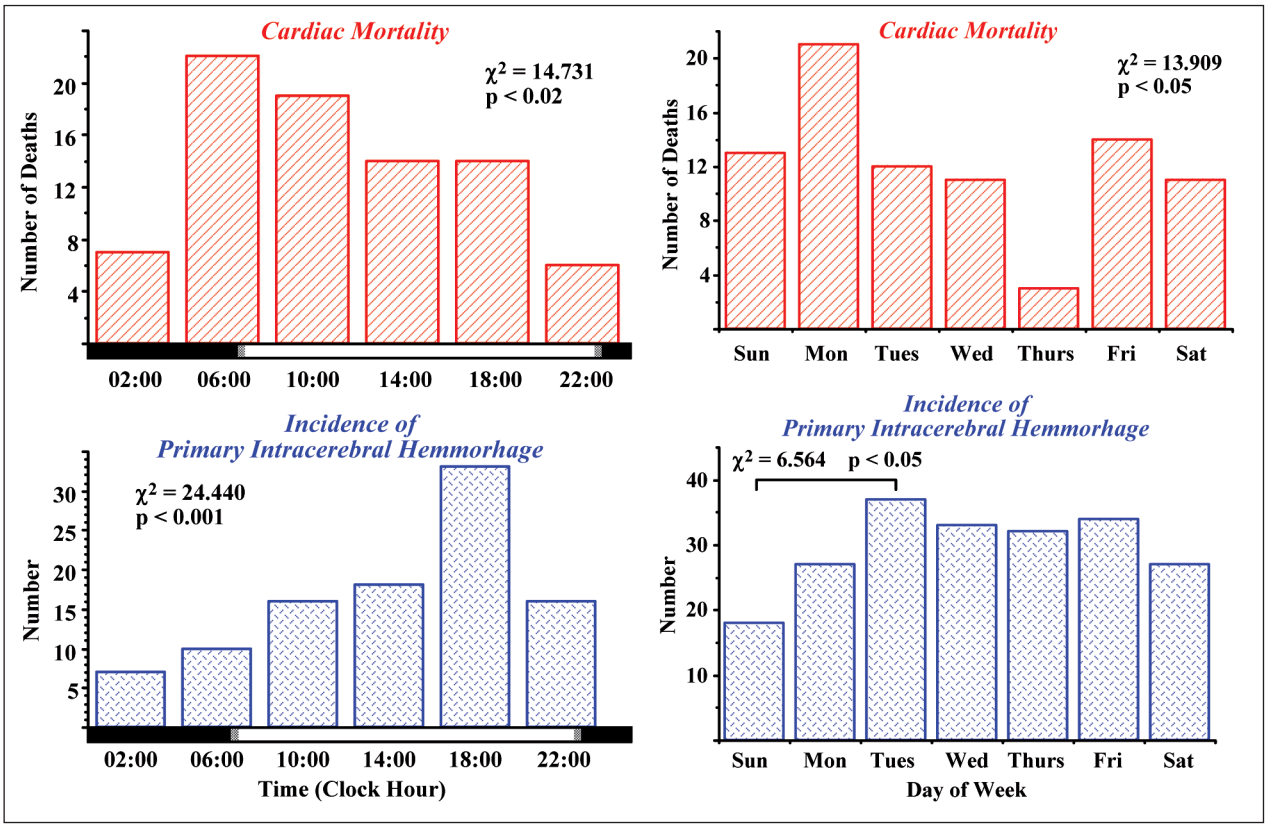

Figure 5: *Circadian (left) and circaseptan (right) variation of cardiac mortality and the incidence of primary intracerebral hemorrhage (redrawn from Nicolau et al., 1991). © American Association for Medical Chronobiology and Chronotherapeutics (AAMCC)*

Cardiac function relies on a time-varying supply of oxidative energy produced by mitochondrial respiration. Mitochondrial dysfunctions in the heart muscle are associated with both structural and functional abnormalities (Kohsaka et al., 2014). Heart function relies on oxidative energy that is supplied continuously by mitochondria. Because energy demand in the heart varies across the sleep/wake cycle, timely supply of energy may benefit the heart and optimize its function. This time-dependent energy metabolism is subject to the circadian clock system, in which a set of core clock genes plays a major role. Without clock gene function, the daily rhythms in heart energy metabolism are impaired. Kohsaka et al. (2014) showed that ablation of the circadian clock gene Bmal1 specific to the heart results in cardiac mitochondrial defects, such as reduced enzymatic activities within the respiratory complex. Mice lacking cardiac Bmal1 function show decreased expression of genes associated with the fatty acid oxidative pathway, the tricarboxylic acid cycle, and the mitochondrial respiratory chain in the heart; and they develop severe progressive heart failure with age. It has also been shown that similar changes in gene expression related to mitochondrial oxidative metabolism occur in C57BL/6J mice subjected to chronic reversal of the light-dark cycle, thus showing disrupted circadian rhythmicity. These findings by Kohsaka et al. (2014) indicate that the circadian clock system plays an important role in coordinating mitochondrial metabolism and thus also in maintaining intact cardiac function.

Mitochondria in Developing and Diseased Heart

The high-capacity mitochondrial system generates and consumes enormous amounts of ATP in order to support the constant pumping function of the heart in response to changing energy demands (Dorn et al., 2015). The development and maturation of this specialized high-capacity mitochondrial

system in the heart occur largely during the perinatal and postnatal developmental stages. The process begins with a major surge in mitochondrial biogenesis at birth. Following this biogenic surge, there is a period of maturation that involves a dramatic increase in dynamics (mitophagy, fusion, and fission), leading to redistribution and dense packing of the specialized mature mitochondria along myofibrils. This cellular architecture facilitates the transfer of high-energy phosphates between the mitochondria and the contractile apparatus. The resultant mature mitochondrial system is capable of high-capacity oxidation of fuels such as fatty acids, the predominant fuel substrate for the adult heart (Dorn et al., 2015). Pathological cardiac hypertrophy and heart failure are characterized by an increase in the expression of many contractile and structural genes that are normally expressed in fetal hearts along with decreased expression of normal adult genes. Results imply progressive, pathologic remodeling and dysregulation of mitochondrial energy production during the development of heart failure (Dorn et al., 2015).

Role of mitochondrial DNA damage in the development of atherosclerosis

The mitochondrial organelles have pivotal roles in producing reactive oxygen species (ROS) and in coordinating cell death, inflammation and metabolism. Mitochondrial dysfunction leads to oxidative stress, disease, cell death, metabolic dysfunction and inflammation, which can all promote atherosclerosis (Yu & Bennet, 2016). Recent evidence indicates that mitochondrial DNA (mtDNA) damage is present and promotes atherosclerosis through mitochondrial dysfunction. mtDNA damage may also be increased in atherosclerosis, since conditions that promote disease, such as hyperglycemia and smoking, also increase ROS. Atherosclerosis, a leading cause of mortality in developed countries, is characterized by fatty plaque formation in the arteries, the large conduit vessels carrying vital oxygen and nutrients to the tissues. The atherosclerotic plaque forms at sites of endothelial dysfunction, often where there is disturbed flow and altered shear stress. However, plaque rupture may occur that occludes the artery, resulting in significant sequelae such as heart attacks and strokes (Yu & Bennett, 2016). Further work needs to be done to see whether eliminating mtDNA damage and mitochondrial dysfunction can reduce atherosclerotic plaque burden and/or vulnerability.

Vital Role for Mitochondrial Calcium Exchange in Heart Function

Luongo et al. (2017) documented that the exit of calcium from mitochondria serves a critical role in heart function. It has long been thought that calcium transport into mitochondria is a key signal linking cardiac workload with energy production (Luongo et al., 2017). Other studies have shown the importance of this pathway during stress, but the question was also raised whether the mitochondrial calcium exchange was necessary for normal cardiac function. Luongo et al. (2017) used a newly developed mutant mouse model to show that a mitochondrial sodium-calcium exchanger (NCLX) is necessary for the heart to function properly. They found that without NCLX, the animals suffered sudden cardiac death. They showed that the movement of calcium in and out of the myocardial mitochondria is important to both cell death and pro-energetic signaling pathways (Luongo et al., 2017). These findings suggest that mitochondrial calcium efflux may be a promising therapeutic target with the potential to lessen the severity of cardiac disease states (Luongo et al., 2017).

Monitoring of Mitochondria may Predict Cardiac Arrest

Perry et al. (2017) developed a new technique to continuously monitor the mitochondria on the epicardial surface using an enhanced resonance Raman spectroscopy which may predict the onset

of cardiac arrest. They have conducted experiments on animals to evaluate whether the live heart tissue is receiving enough oxygen to meet the demands in the heart. They identified the time when the myocardium is so energy deficient that it cannot function properly with changes in mitochondrial redox state preceding changes in cellular function. Whereas most blood tests used presently only measure tissue injury or ischemia, this new approach evaluates the entire mitochondrial electron transport chain to determine how much oxygen a cell needs to function properly (Perry et al., 2017). These authors were able to quantify the reduced fraction of specific electron transport chain cytochromes, a metric they named the resonance Raman reduced mitochondrial ratio (3RMR). As oxygen deficiency worsens, heme moieties within the electron transport chain become progressively more reduced, leading to an increase in 3RMR. Myocardial 3RMR increased from reference values after inferior vena cava occlusion (Perry et al., 2017). A 3RMR value exceeding 40% at 10 min predicted subsequent cardiac arrest with 95% sensitivity and 100% specificity, outperforming all current measures, including contractility and ejection fraction. 3RMR correlated with indices of intracellular redox state and energy production (Perry et al., 2017). This new method may allow the assessment of the adequacy of oxygen delivery to tissues in patients during intensive care medicine and surgery.

Concluding Remarks

Rhythms are ubiquitous and important to all living organisms. Rhythms are affected externally by the environment, activity schedule and diet, among other factors. Rhythms are also partly endogenous. Mitochondria also play an important role in the body and can influence biological rhythms via circadian clock genes. Biological rhythms are important for health. Circadian disruption and impaired clock genes are associated with increased cardiovascular disease risk and actual disease. Circadian rhythm characteristics serve as markers of health and disease. They lead to primary prevention and, when needed, they can guide the timing of treatment (chronotherapy). New treatment modalities of mitochondrial dysfunctions (e.g., CoQ10 supplementation) should be combined with chronobiology for optimal results in cardiovascular and other diseases.

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Seven Day Blood Pressure Variability: The Effect of Sauna Procedure and Whole Body Cryotherapy Procedure on 24 Hour Blood Pressure Profile in Healthy Subjects

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Introduction

Regular exercise increases life expectancy, quality of life and work capability and productivity. In patients with ischemic heart disease the non-pharmacologic exercise treatment decrease morbidity and mortality of patients. Exercise is an easily accessible and inexpensive approach to improve cardiovascular health, control weight gain, and increase survival chances after a morbid event such as a myocardial infarction. It is, however, sometimes associated with untoward effects in vulnerable subjects. A contributory factor may be heart rate variability, which in the long-term is increased in association with exercise, but may be decreased in the short-term during exercise and the recovery span after exercise (1-4).

Because there are not many data about the effect of one hour aerobic and resistant training on 24h profiles of systolic and diastolic blood pressure, measured using ambulatory blood pressure monitoring, in the days with exercise and in the days without exercise during seven day ambulatory blood pressure monitoring we studied it.

We have found that in healthy subjects one hour lasting aerobic training, combined training does not change mean blood pressure from seven day/ 24h ambulatory blood pressure monitoring and there were no differences between the days with exercise and without exercise in healthy subjects (5) and in patients with coronary heart disease one hour lasting combined training (aerobic and resistant) does not change mean blood pressure from seven day/ 24h ambulatory blood pressure monitoring.

Our previous studies on 7 day /24 h ambulatory blood pressure monitoring showed that the values of 24h blood pressure varies from day to day in the same healthy men and patients (6-10). In physiotherapy there are used positive and negative thermotherapy in the application on the whole body in the regeneration of the tissues in organism and also in the therapy of diseases.

A lot of studies analyzed the immediate effect of the sauna procedure - positive thermotherapy on the whole body and cryotherapy procedure on the whole body- negative thermotherapy on cardiovascular parameters - on blood pressure and heart rate.

A sauna bath exposes the bather to a short period of intense dry or wet heat and thus activates the sympathetic nervous system (11). To prevent an increase in the core body temperature, blood is diverted to the skin to allow cooling to take place. Heart rate is elevated, and in particular diastolic blood pressure decreases as a result of a lower peripheral resistance (12).

There are no data about the effects of these procedures on 24-hour blood pressure profile in the days with procedures of sauna and the days without procedure and in the days with procedure of cryotherapy and in the days without cryotherapy.

The aim of the study was to compare 24-hour profile from the 7-day blood pressure monitoring after application of sauna procedure and cryotherapy procedure in healthy subjects. From seven day ambulatory blood pressure monitoring we compared the blood pressure 24 h profile in the day with sauna procedure (0-24 h) and in the day without sauna procedure (25-48 h after sauna procedure). We analyzed also the effect of whole body cryotherapy on the same day blood pressure profile (0-24 h) and on the next day blood pressure profile (25-48) without cryotherapy during seven days /24h ambulatory blood pressure monitoring in healthy subjects.

Methods and subjects

We examined 10 men and 10 women, healthy subjects, mean age 25±0.5 years, body weight was 70±6.50 kg, height was 1.74±0.044 m, body mass index (BMI) 23±0.705 kg/m2.

Sauna procedure

The sauna culture has always flourished in Finland and nowadays is used everywhere. Taking a sauna begins by washing oneself up and then going to sit for some time in the hot room, typically warmed to 80–110 ˚C (176–230 ˚F). The subject after rewarming takes cooling in water. After cooling one goes back to the hot room and begins the cycle again. The healthy young subjects took two cycles of warming and cooling.

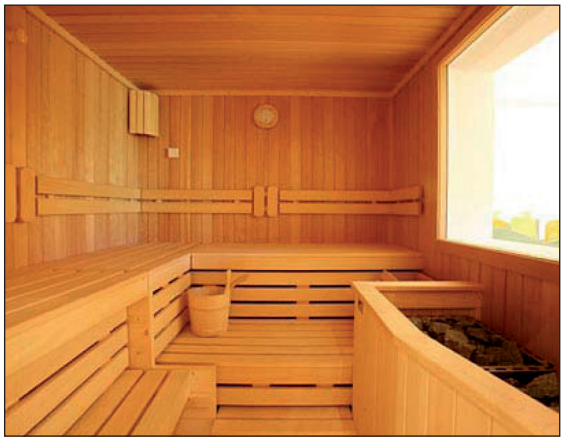

Figure 1: *Sauna*

Whole body cryotherapy

Whole body cryotherapy (WBC) is currently used in physiotherapy. This treatment involves exposing individuals to extremely cold dry air (below -100 ˚C) for two to four minutes. During these exposures, individuals wear minimal clothing, which usually consists of shorts for males and shorts and a crop top for females. After two to four minutes cooling there is a period of aerobic exercise for a period of 10 minutes.

Figure 2: *Whole body cryotherapy*

Methods of ambulatory blood pressure monitoring

The subjects were recruited for seven-day blood pressure monitoring. Medical Instruments (A&D, Japan) were used for ambulatory blood pressure monitoring (oscillation method). One-hour means of systolic and diastolic blood pressure were evaluated. We calculated mean systolic and diastolic blood pressure for seven days. The regime of measurement of blood pressure was done for 7 days repeatedly every 30 minutes from 5 to 22 h during the day time and once in an hour from 22 to 5 h at night (7).

For the sauna procedure and cryotherapy procedure they took the instruments for ambulatory blood pressure monitoring off. The average SBP and DBP and their standard deviations (SD) or standard error (ER) in the given days were determined by the calculation of arithmetic mean of these values during every day and during 7 days. We evaluated the days with sauna (0-24h) and the days without sauna (25-48h) and the days with cryotherapy (0-24 h) and the days without cryotherapy (25 -48 h). The study was approved by local ethics committee and the patients signed the informed consent.

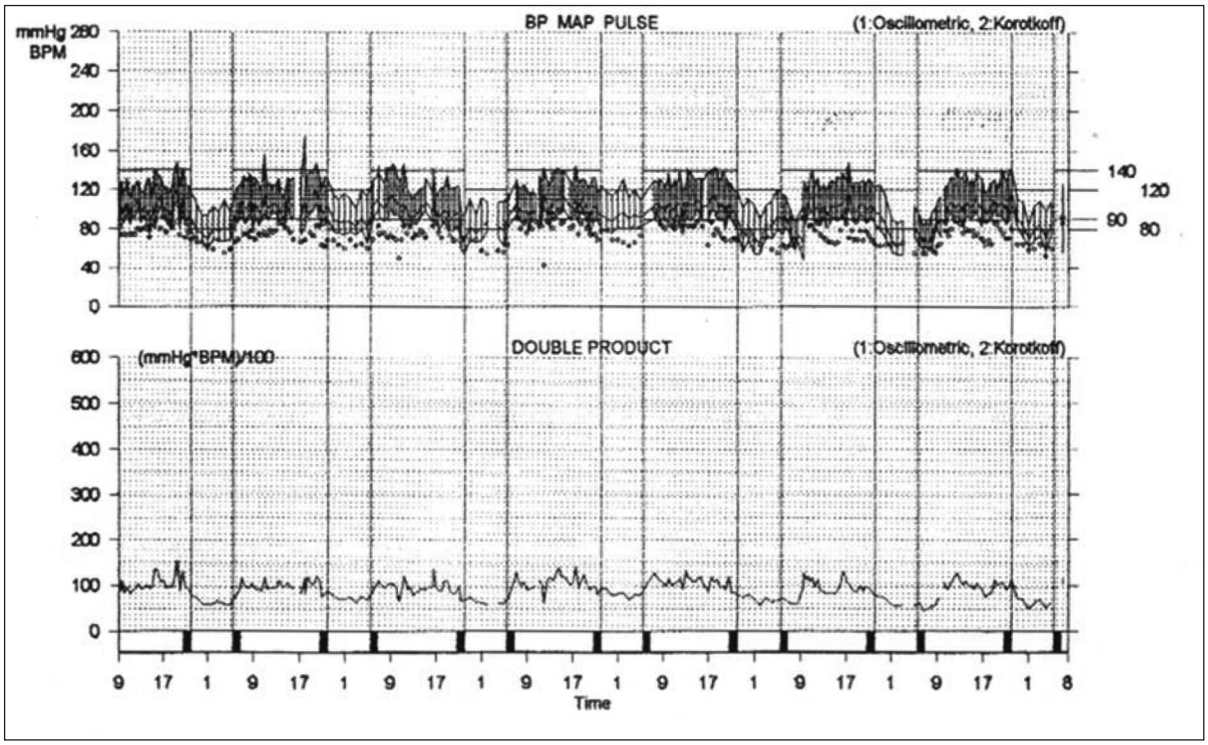

Figure 3: *Seven day ambulatory blood pressure monitoring*

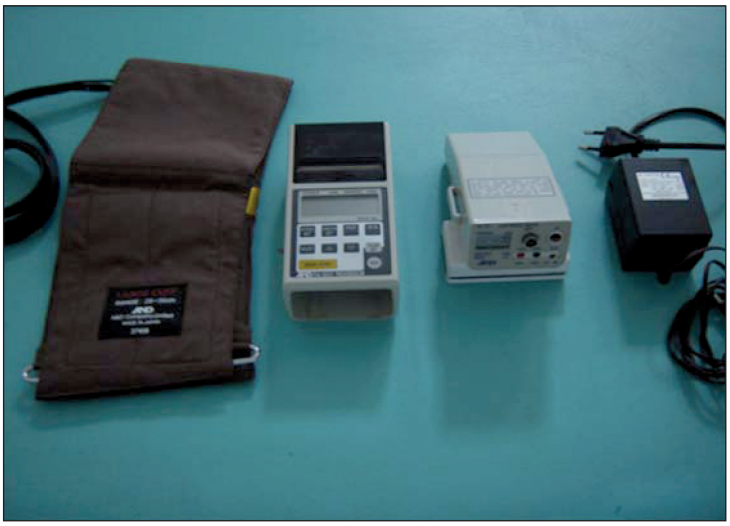

Figure 4: *Blood pressure monitoring device A and D*

Results

In the group of healthy subjects seven day ambulatory monitoring in all seven days including one day with sauna and one day with cryotherapy showed the mean systolic blood pressure SD 122 ± 7.2 mmHg, the mean diastolic blood pressure 71 ± 2.8 mmHg and heart rate 73 ± 6.2 beat per minute. The data are presented in Fig. 5 – 7.

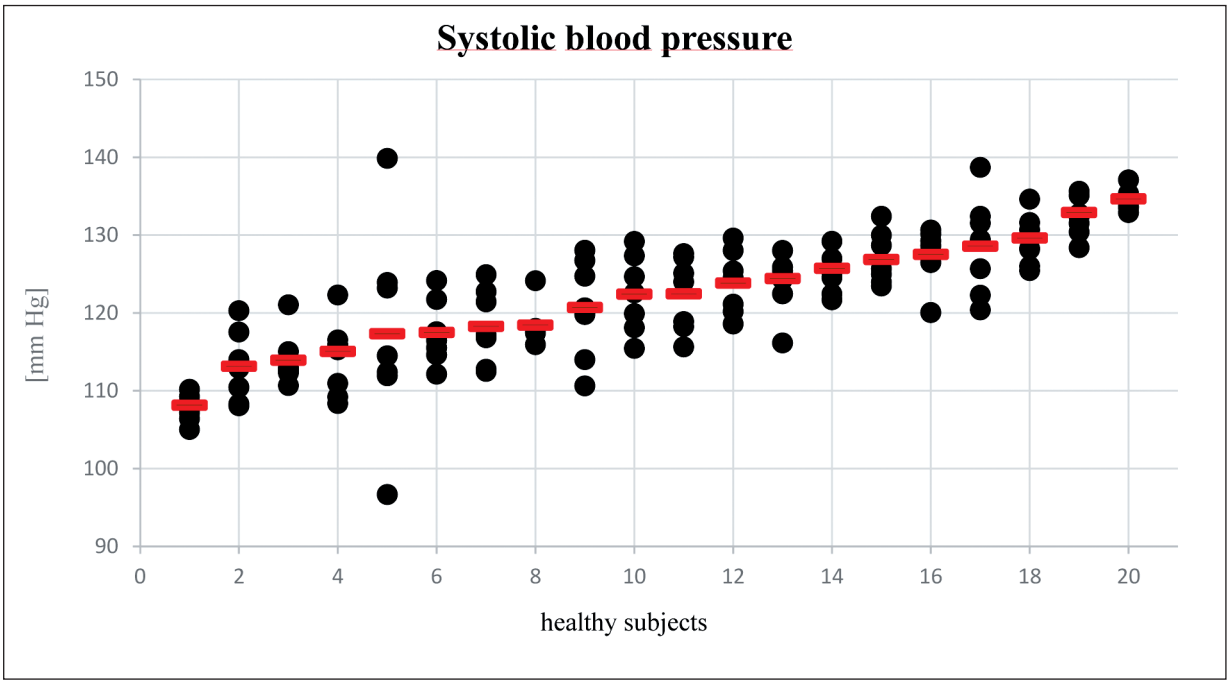

Figure 5: *Mean systolic blood pressure from 7 day ambulatory blood pressure monitoring in all seven days including one day with sauna and one day with cryotherapy is shown as red lines, 24-hour blood pressure profile in 7-days is shown as black point*

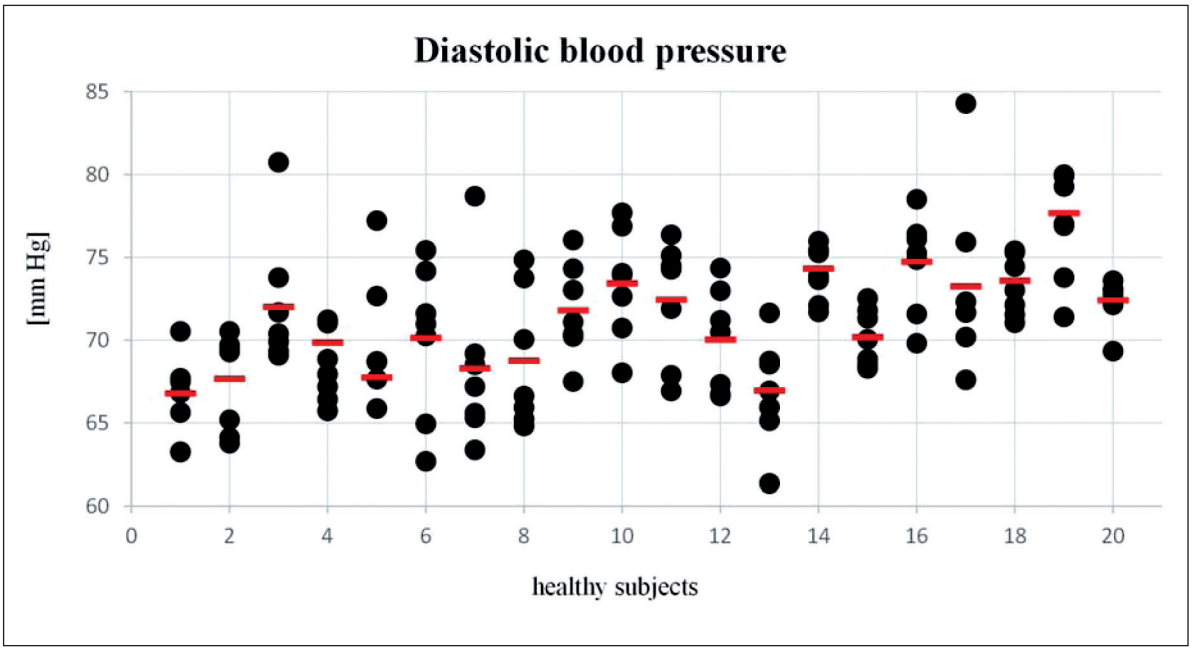

Figure 6: *Mean diastolic blood pressure from 7 day ambulatory blood pressure monitoring in all seven days including one day with sauna and one day with cryotherapy is shown as red lines, 24-hour blood pressure profile in 7-days is shown as black point*

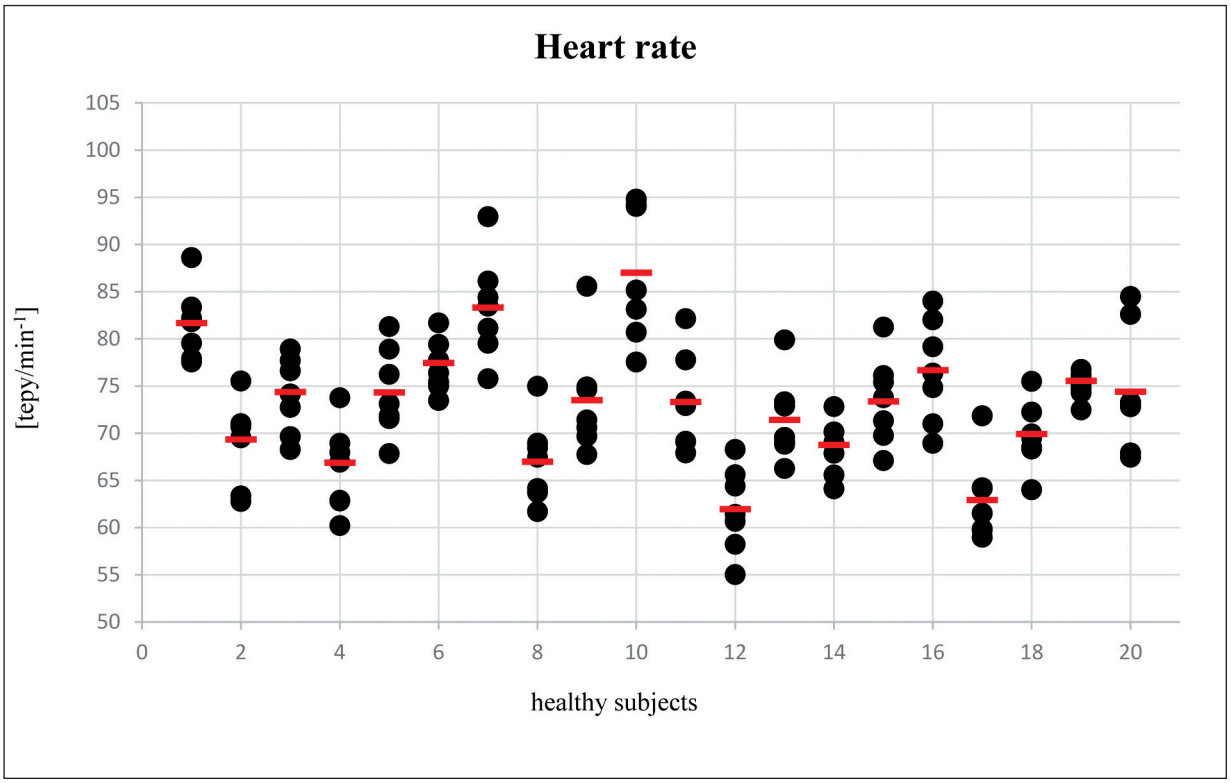

Figure 7: *Mean heart rate from 7 day ambulatory blood pressure monitoring in all seven days including one day with sauna and one day with cryotherapy is shown as red lines, 24-hour heart rate profile in 7-days is shown as black point*

Sauna

We compared mean systolic blood pressure (±SD) from 7 day ambulatory blood pressure monitoring in all seven days (122±7.2 mmHg) with mean systolic blood pressure profile (±SD) 0 – 24 h after sauna (121± 9 mmHg) and with mean systolic blood pressure profile (±SD) 25 – 48 h after sauna (122±9.3 mmHg) and we have not found differences in systolic blood pressure. These results are shown in Fig 8.

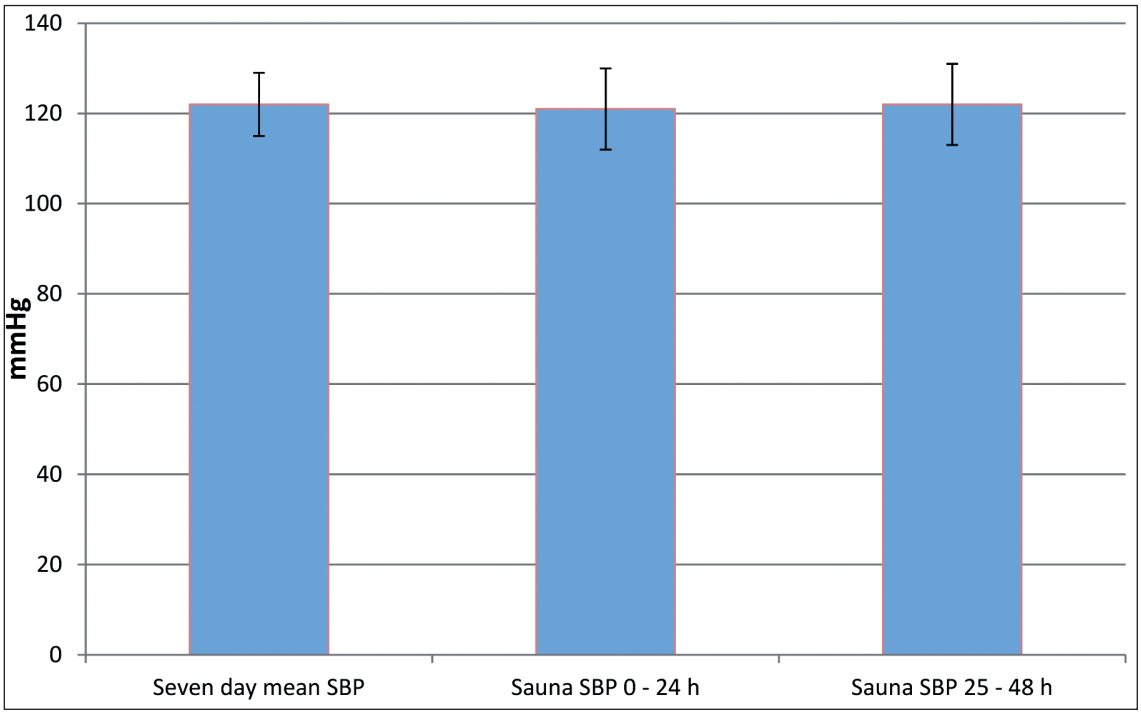

Figure 8: *Mean systolic blood pressure (±SD) from 7 day ambulatory blood pressure monitoring in all seven days, mean systolic blood pressure (±SD) 0 – 24 h after sauna, mean systolic blood pressure (±SD) 25 – 48 h after sauna*

We compared mean diastolic blood pressure (±SD) from 7 day ambulatory blood pressure monitoring in all seven days (71±2.8 mmHg) with mean diastolic blood pressure profile (±SD) 0 – 24 h after sauna (70±4.69 mmHg) and with mean diastolic blood pressure profile (±SD) 25 – 48 h after sauna (70±5.4 mmHg) and we have not found differences in diastolic blood pressure. These results are shown in Fig 9.

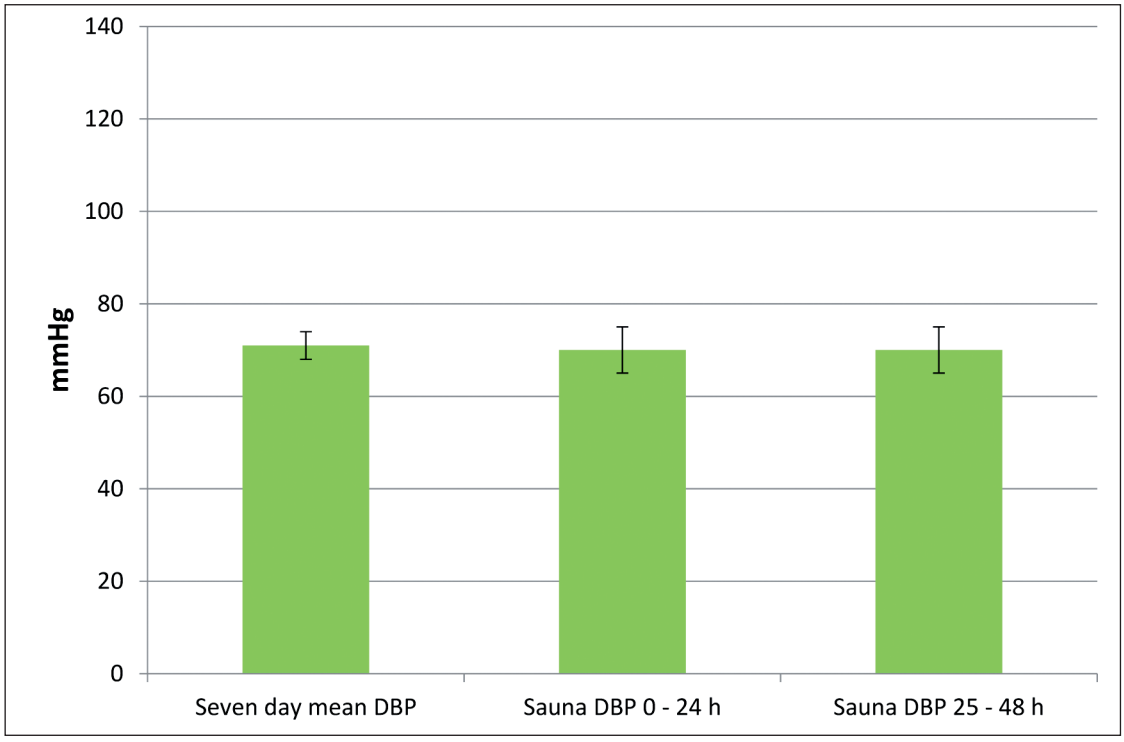

Figure 9: *Mean diastolic blood pressure from 7 day ambulatory blood pressure monitoring in all seven days, mean diastolic blood pressure (±SD) 0 – 24 h after sauna, mean diastolic blood pressure (±SD) 25 – 48 h after sauna*

We compared mean heart rate (±SD) from 7 day ambulatory blood pressure monitoring in all seven days (73±6.2 bpm) with mean heart rate (±SD) 0 – 24 h after sauna (75±9.0 bpm) and with mean heart rate (±SD) 25 – 48 h after sauna (72±6.1 mmHg) and we have not found differences in heart rate. These results are shown in Fig 10.

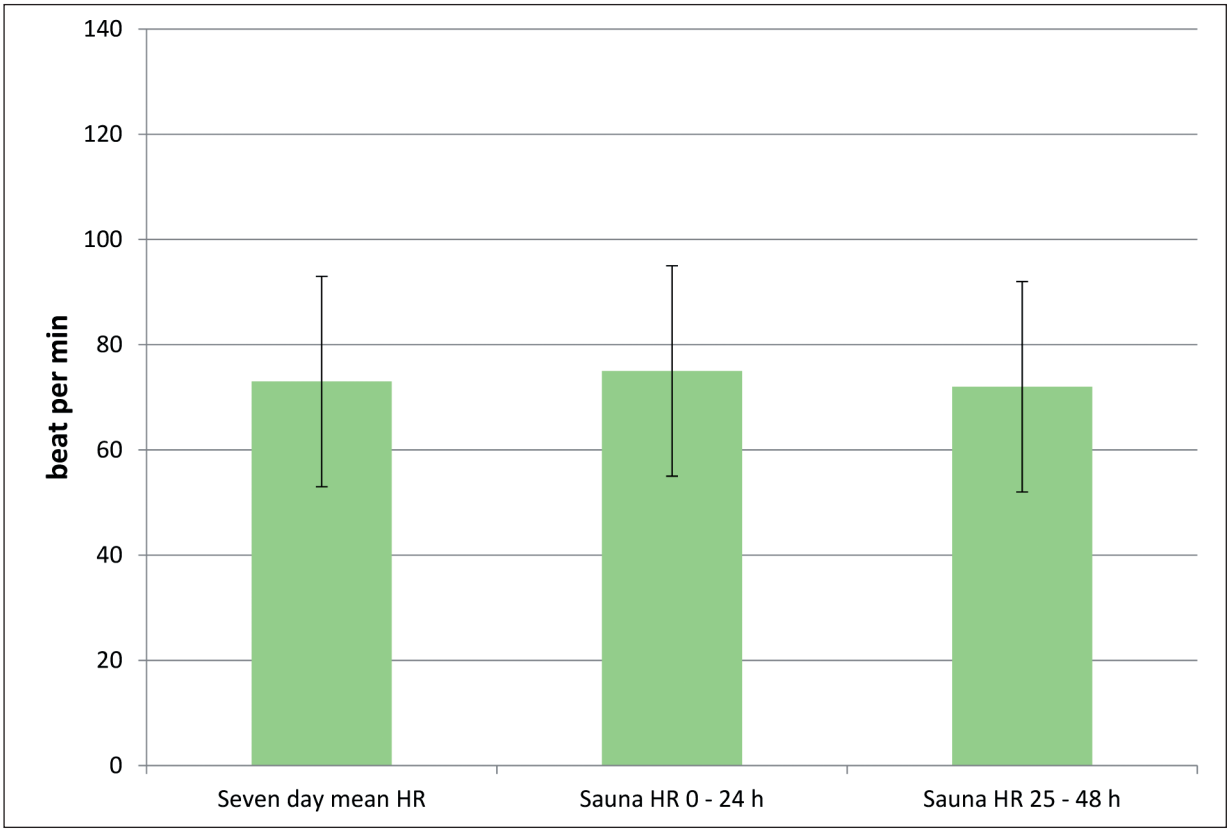

Figure 10: *Mean heart rate from 7 day ambulatory blood pressure monitoring in all seven days, mean heart rate (±SD) 0 – 24 h after sauna, mean heart rate (±SD) 25 – 48 h after sauna*

Cryotherapy

After cryotherapy we compared mean systolic blood pressure (±SD) from 7 day ambulatory blood pressure monitoring in all seven days (122±7.2 mmHg) with mean systolic blood pressure profile (±SD) 0 – 24 h after cryotherapy (122±8.8mmHg) with mean systolic blood pressure profile (±SD) 25 – 48 h after cryotherapy (121±8.1mmHg) and we have not found differences in systolic blood pressure after cryotherapy. These results are shown in Fig 11.

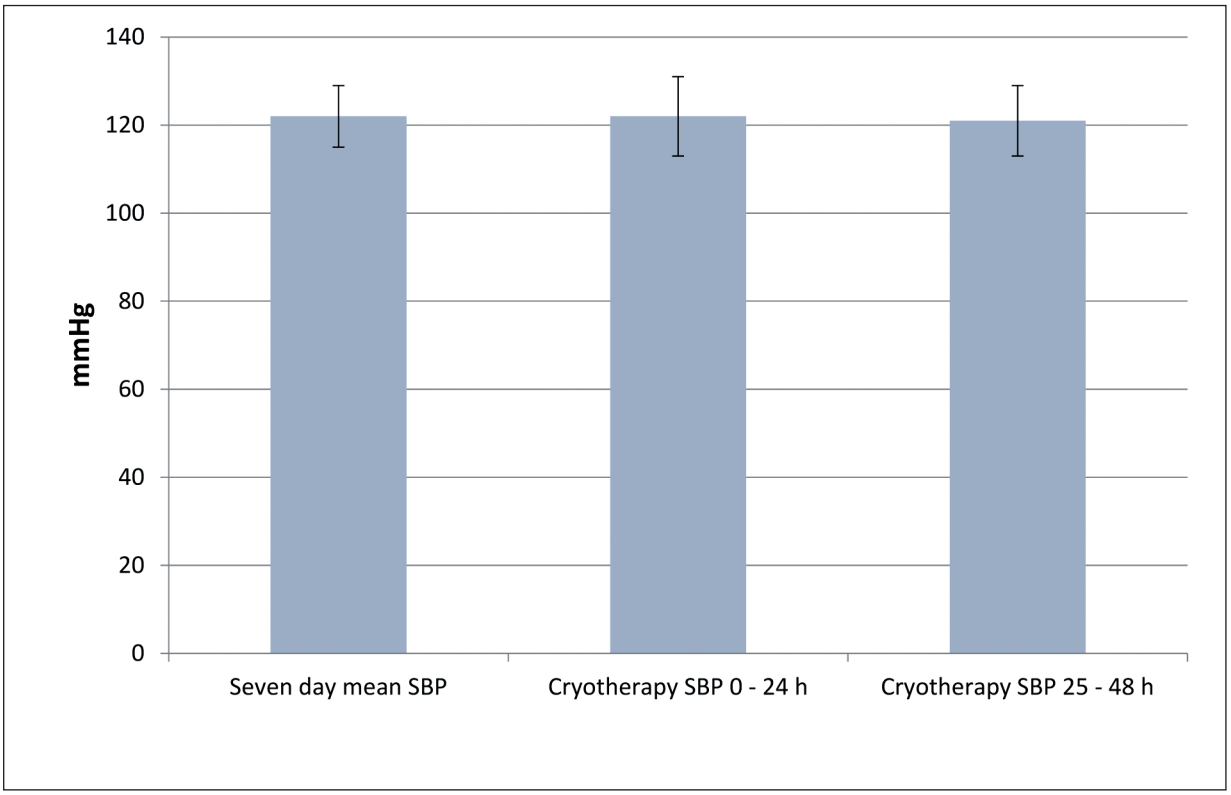

Figure 11: *Mean systolic blood pressure (±SD) from 7 day ambulatory blood pressure monitoring in all seven days, mean systolic blood pressure (±SD) 0 – 24 h after cryotherapy, mean systolic blood pressure (±SD) 25 – 48 h after cryotherapy*

After cryotherapy we compared mean diastolic blood pressure (±SD) from 7 day ambulatory blood pressure monitoring in all seven days (71±2.8 mmHg) with mean diastolic blood pressure profile (±SD) 0 – 24 h after cryotherapy (71±5.4mmHg) with mean diastolic blood pressure profile (±SD) 25 – 48 h after cryotherapy (71±3.6mmHg) and we have not found differences in diastolic blood pressure after cryotherapy. These results are shown in Fig 12.

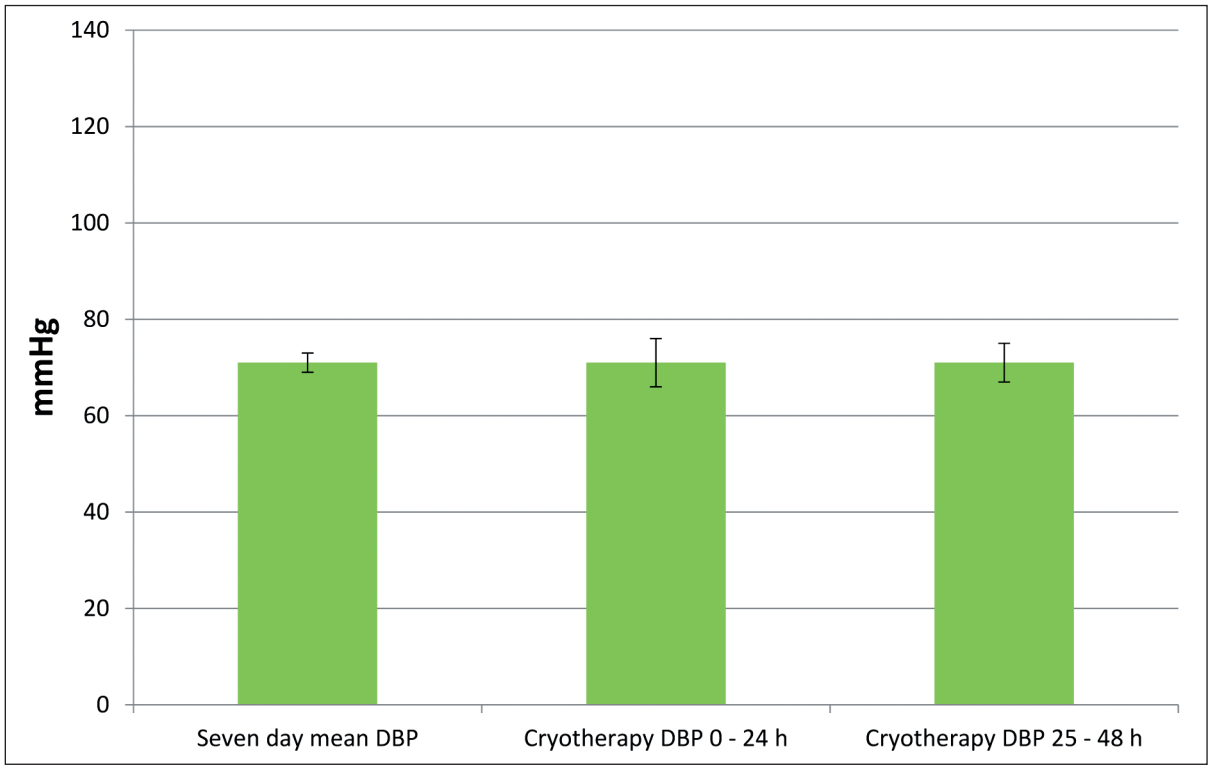

Figure 12: *Mean diastolic blood pressure from 7 day ambulatory blood pressure monitoring in all seven days, mean diastolic blood pressure (±SD) 0 – 24 h after cryotherapy, mean diastolic blood pressure (±SD) 25 – 48 h after cryotherapy*

After cryotherapy we compared mean heart rate (±SD) from 7 day ambulatory blood pressure monitoring in all seven days (73±6.2 bpm) with mean heart rate (±SD) 0 – 24 h after cryotherapy (74±9.2 bpm) and with mean heart rate (±SD) 25 – 48 h after cryotherapy (71±7.3 bpm) and we have not found differences in heart rate after cryotherapy. These results are shown in Fig 13.

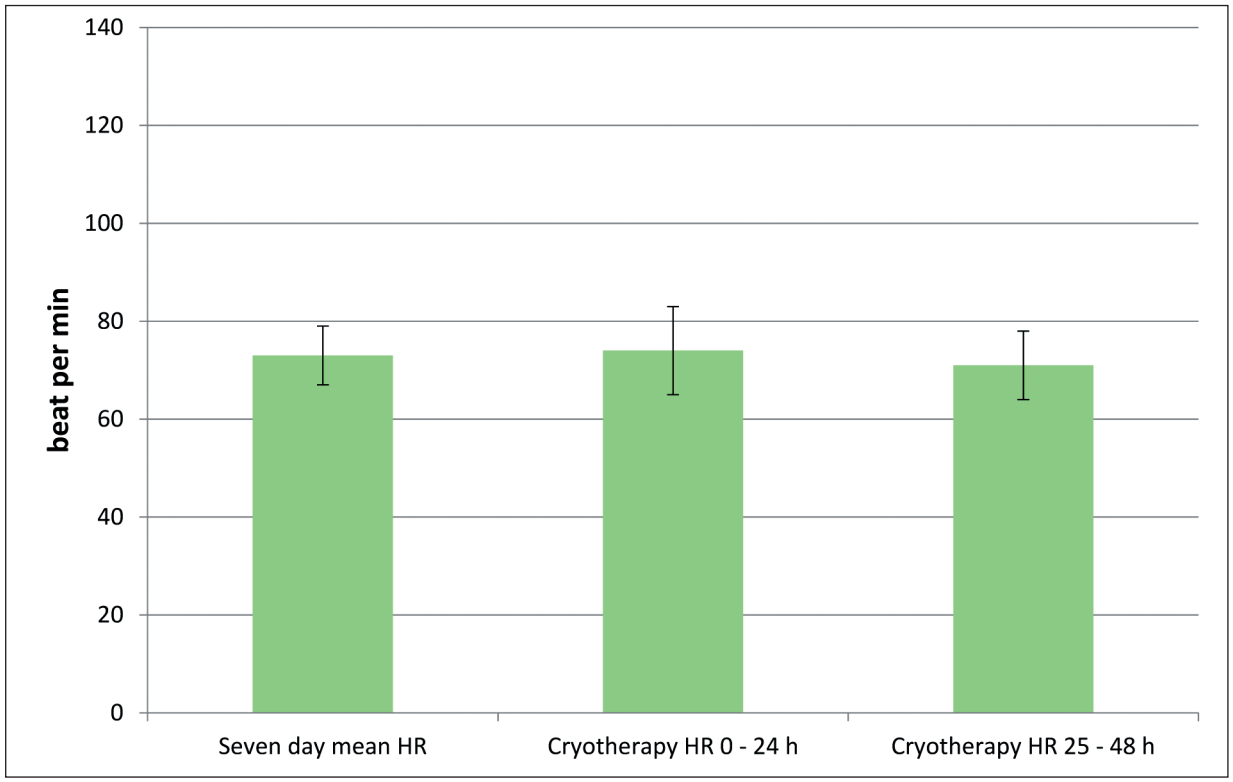

Figure 13: *Mean heart rate from 7 day ambulatory blood pressure monitoring in all seven days, mean heart rate (±SD) 0 – 24 h after cryotherapy, mean heart rate (±SD) 25 – 48 h after cryotherapy*

Sauna

The variability of 24 h systolic blood pressure in the day after sauna (0-24h) and of 24 h systolic blood pressure after sauna (25-48h) was not different in comparison to the seven day mean systolic blood pressure, as is shown on Fig.14.

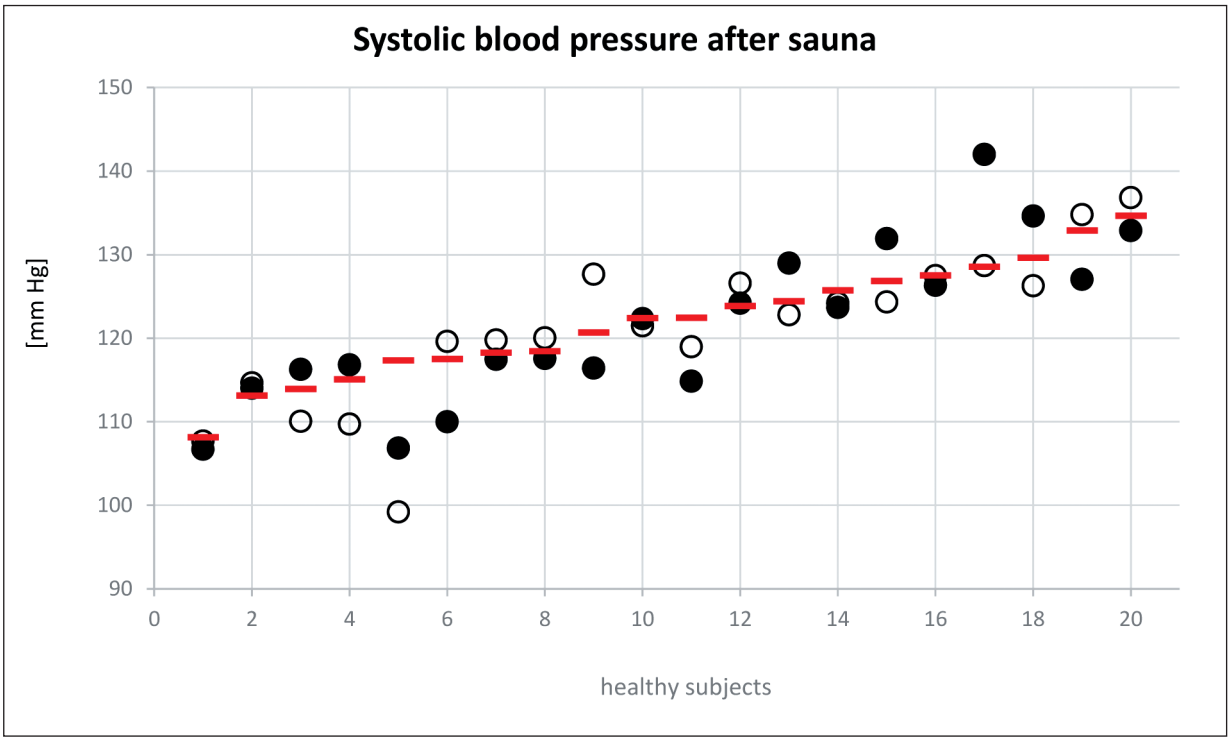

Figure 14: *Mean systolic blood pressure from 7 day ambulatory blood pressure monitoring in all seven days (red lines), mean systolic blood pressure in day after sauna 0 – 24 h (open circles), mean systolic blood pressure in day after sauna 25 – 48 h (black points)*

The variability of 24 h diastolic blood pressure in the day after sauna (0-24h) and of 24 h diastolic blood pressure after sauna (25-48h) was not different in comparison to the seven day mean diastolic blood pressure, as is shown on Fig.15.

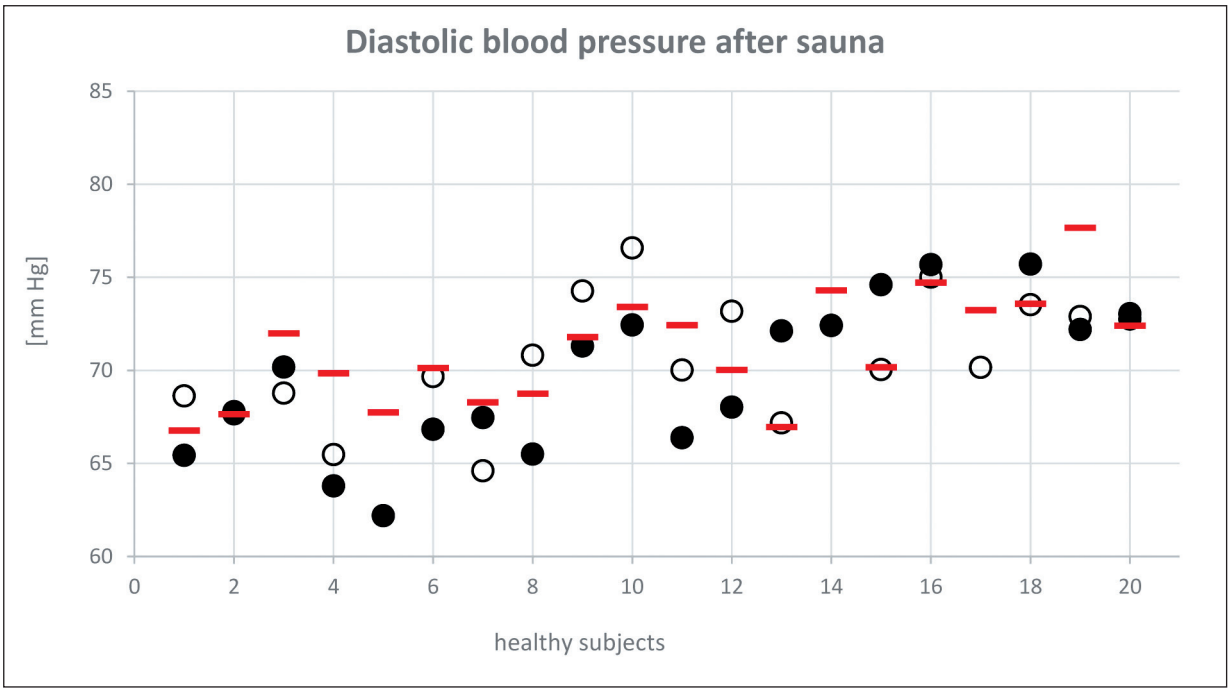

Figure 15: *Mean diastolic blood pressure from 7 day ambulatory blood pressure monitoring in all seven days (red lines), mean diastolic blood pressure in day after sauna 0 – 24 h (open circles), mean diastolic blood pressure in day after sauna 25 – 48 h (black points)*

The variability of 24 h heart rate in the day after sauna (0-24h) and of 24 h heart rate after sauna (25-48h) was not different in comparison to the seven day mean heart rate, as is shown on Fig. 16.

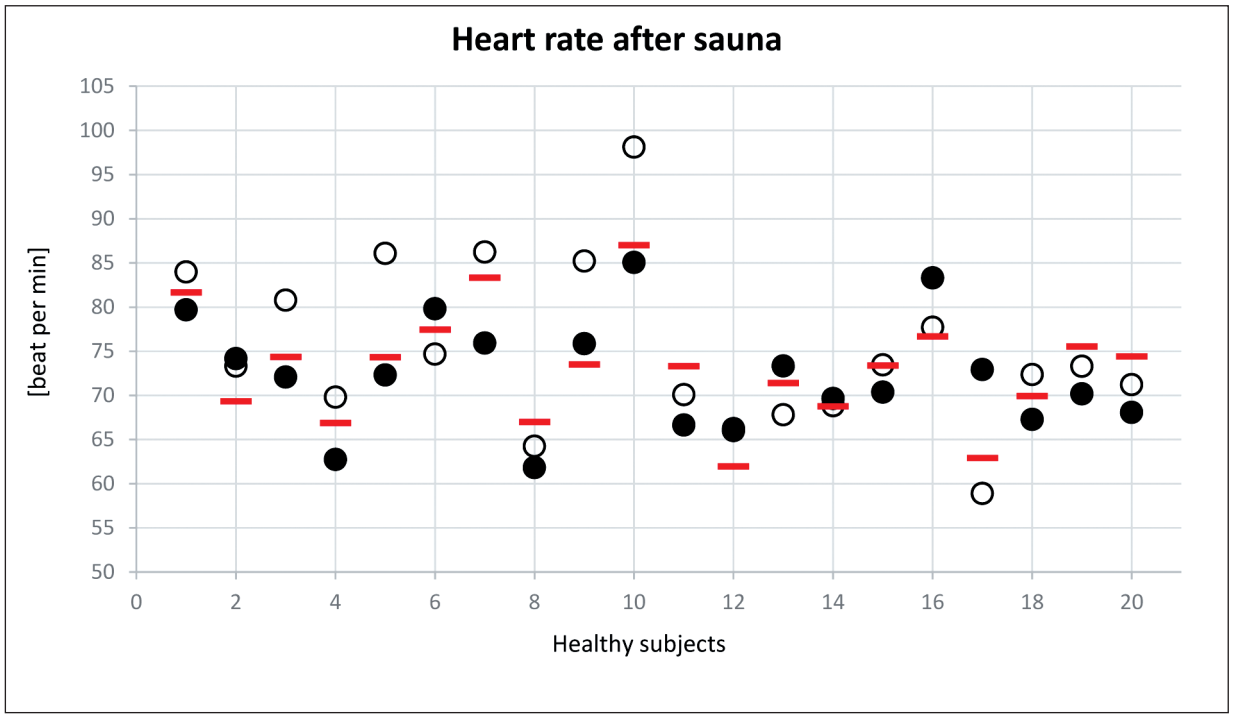

Figure 16: *Mean heart rate from 7 day ambulatory blood pressure monitoring in all seven days (red lines), mean heart rate in day after sauna 0 – 24 h (open circles), mean heart rate in day after sauna 25 – 48 h (black points)*

Cryotherapy

The variability of 24 h systolic blood pressure in the day after cryotherapy (0-24h) and of 24 h systolic blood pressure after cryotherapy (25-48h) was not different in comparison to the seven day mean systolic blood pressure, as is shown on Fig.17.

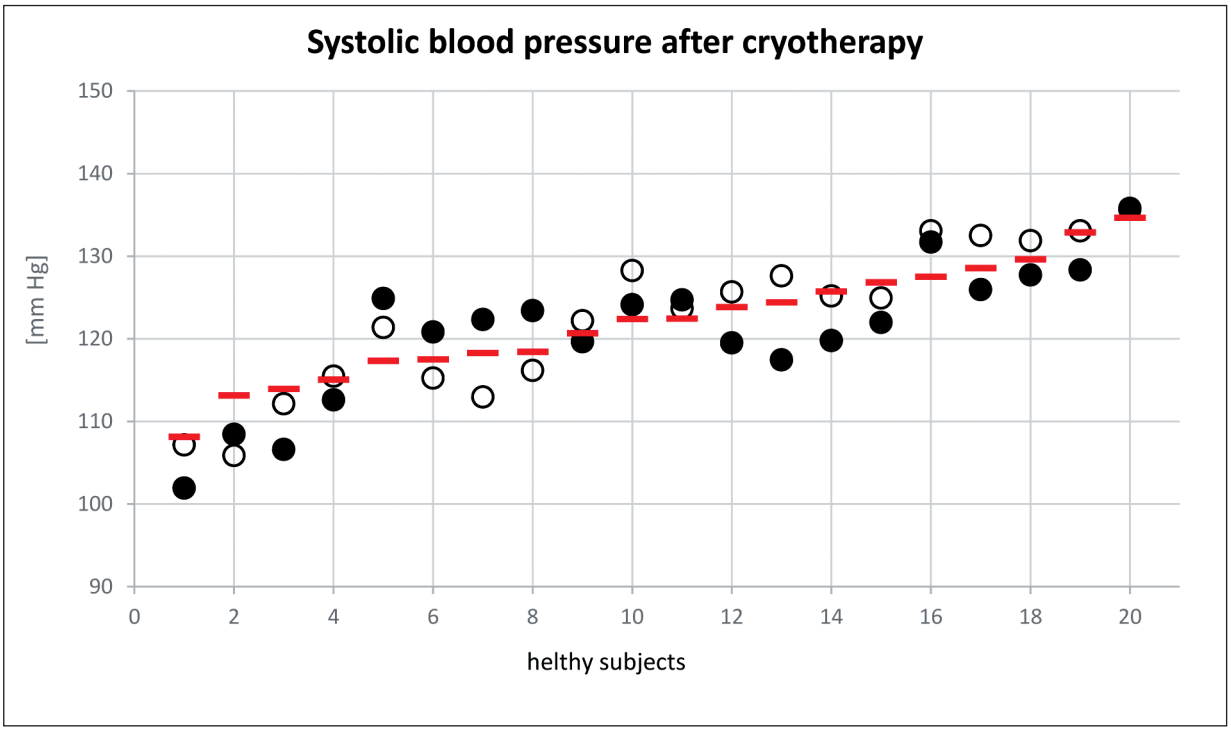

Figure 17: *Mean systolic blood pressure from 7 day ambulatory blood pressure monitoring in all seven days (red lines), mean systolic blood pressure in day after cryotherapy 0 – 24 h (open circles), mean systolic blood pressure in day after cryotherapy 25 – 48 h (black points)*

The variability of 24 h diastolic blood pressure in the day after cryotherapy (0-24h) and of 24 h diastolic blood pressure after cryotherapy (25-48h) was not different in comparison to the seven day mean diastolic blood pressure, as is shown on Fig. 18.

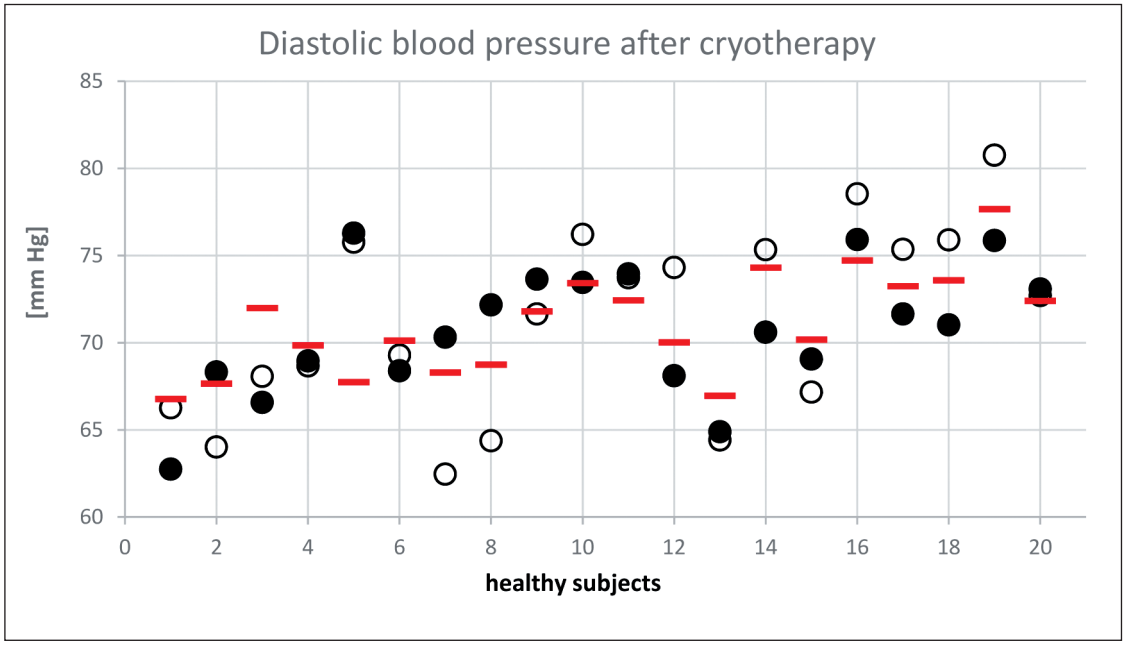

Figure 18: *Mean diastolic blood pressure from 7 day ambulatory blood pressure monitoring in all seven days (red lines), mean diastolic blood pressure in day after cryotherapy 0 – 24 h (open circles), mean diastolic blood pressure in day after cryotherapy 25 – 48 h (black points)*

The variability of 24 h heart rate in the day after cryotherapy (0-24h) and of 24 h heart rate after cryotherapy (25-48h) was not different in comparison to the seven day mean heart rate, as is shown on Fig. 19.

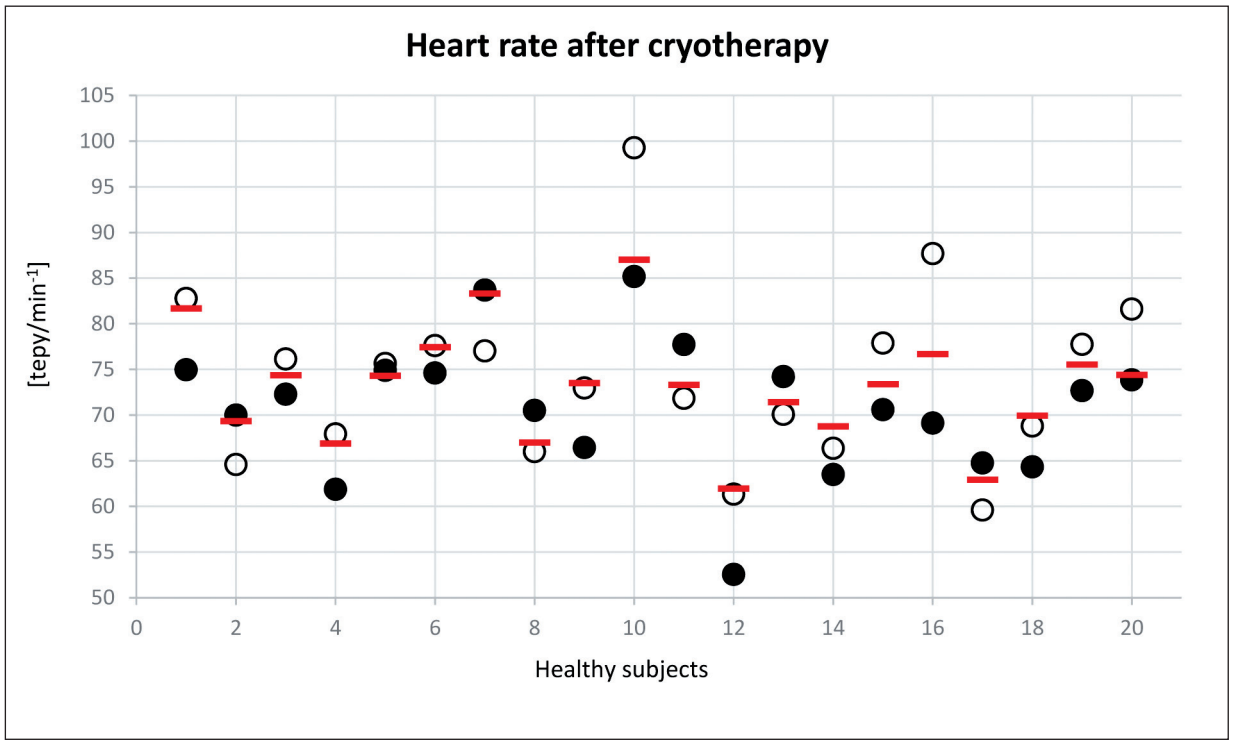

Figure 19: *Mean heart rate from 7 day ambulatory blood pressure monitoring in all seven days (red lines), mean heart rate in day after cryotherapy 0 – 24 h (open circles),mean heart rate in day after cryotherapy 25 – 48 h (black points)*

Discussion

Systemic thermal therapy, so-called Sauna or warm water insertion therapy, which is considered to be one of the thermal vasodilatation therapies and has been applied to many healthy people for centuries, has been gathering attention from various medical fields. There have been reviews of the physiologic effects, benefits and risks of sauna bathing (13, 14).

Sauna effects the cardiovascular parameters. To prevent an increase in the core body temperature, blood is diverted to the skin to allow cooling to take place. Heart rate is elevated, and in particular diastolic blood pressure decreases as a result of a lower peripheral resistance. Among healthy people, a sauna bath does not usually cause excess cardiovascular strain, as has been indicated by moderate changes in heart rate, blood pressure and the excretion of catecholamines (15, 16).

Our results showed that MESOR of 7day/24-hour systolic blood pressure from 7 day ambulatory blood pressure monitoring was not different from MESOR of systolic blood pressure profile in the day with sauna (0 – 24 h) and from MESOR of systolic blood pressure profile without sauna (25 – 48 h after sauna). Similar results we have find in diastolic blood pressure.

MESOR of diastolic blood pressure from 7 day/24-h ambulatory blood pressure monitoring was not different from MESOR of diastolic blood pressure profile (0 – 24 h) and from MESOR of diastolic blood pressure profile (25 – 48 h after sauna).

Our results showed that heart rate from 7 day/24-h of ambulatory blood pressure monitoring was not different from MESOR of heart rate (0 – 24 h) and from MESOR of heart rate (25 – 48 h after sauna). In healthy subjects our findings are in agreement with the others references (15, 16).

Numerous studies have accumulated scientific evidence supporting the beneficial effect of whole body cryotherapy as an alternative treatment and rehabilitation technique.

The physiological mechanisms responsible for the effect of extreme cold exposure and the scientific basis for and optimal cryotherapy remain unclear. It was showed that stimulation of the autonomic nervous system after a single whole-body cryostimulation was more pronounced by using a cryochamber system (-110° C), (17, 18).

The results in our study showed that in healthy subjects the effect of sauna and cryotherapy does not change 24-hour MESOR of blood pressure profile, evaluated from seven day/ 24-hour ambulatory blood pressure monitoring. On the basis of our results, we can prescribe a cryotherapy in healthy subjects and sport recovery and to enhance sleep quality and biological rhythmic control of human body.

Conclusion

The present study confirms that in healthy subjects the effect of sauna and cryotherapy does not change 24-hour MESOR of blood pressure profile, evaluated from seven day/ 24-hour ambulatory blood pressure monitoring.

The variability of 24-hour blood pressure profile and heart rate in the day after sauna and cryotherapy (0-24h) was not different from resting day in 24-hour values after sauna and cryotherapy (25-48h).

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Seven-Day Ambulatory Blood Pressure Monitoring after 4 Months of Exercise Training

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Introduction

Franz Halberg and Germaine Cornelissen using ambulatory blood pressure monitoring showed the need to account for day-to-day changes of blood pressure and heart rate and the necessity for circadian assessment of the hour-to- hour variability in cardiovascular parameters. Together with the Chronobiology center of Minnesota we participate in the international project BIOCOS. The presentation in May 2017 adds new results to this project BIOCOS (1, 2). In the guidelines for diagnoses of hypertension, fixed limits of 140/90 mmHg (systolic/diastolic BP) were used to diagnose hypertension in all adults 18 years and older. The circadian rhythm in BP was thought to primarily reflect the rest-activity schedule rather than being in part endogenous (2). While this is no longer the case, ambulatory BP monitoring is still restricted to "special cases", often limited to 24 hours. Evidence is presented herein for the need to routinely screen for BP and heart rate (HR) variability, and for continued monitoring in patients in need of treatment. According to a consensus meeting held at St. Anna Hospital, Masaryk Univesity, Brno, Czech Republic in 2008 Franz Halberg with Germaine Cornélissen, Thomas Kenner, Bohumil Fiser, Jarmila Siegelova and others proclaimed Vascular Variability Disorders. Determination of Vascular Variability Disorders – MESOR hypertension, circadian hyper-amplitude-tension, excessive pulse pressure, deficient heart variability and deviation of circadian rhythm is best to diagnose from seven day/24-h ambulatory blood pressure monitoring (3, 4, 5, 6).

Our previous studies analyzed from seven day/24-h ambulatory blood pressure monitoring immediate effect of exercise on circadian blood pressure profile. The question of long exercise during 3-4 months will show the effect on seven day/24-h ambulatory blood pressure monitoring.

The purpose of the study

The aim of the study was to compare the 7-day/24-h blood pressure monitoring before and after exercise training lasting 4 months in healthy subjects.

Methods

We examined 20 healthy subjects, mean age 23.1±2.2 years (from 19 to 29 years, 7 men and 13 women), mean body weight was 72.8±13.4 kg, mean height 174±8 cm.

For exercise training we used walking activity at the level of 70 % maximum heart rate. The exercise training lasted 4 months. The subjects were recruited for seven-day ambulatory blood pressure monitoring before and after 4 months. Medical Instruments TM2431 (A&D, Japan) were used for

ambulatory blood pressure monitoring (oscillation method). One-hour means of systolic and diastolic blood pressure were evaluated. We calculated mean systolic and diastolic blood pressure for seven days and every 24-hour profile.

The regime of measurement of blood pressure was done for 7 days repeatedly every 30 minutes from 5 to 22 h during the day time and once in an hour from 22 to 5 h at night.

The study was approved by local ethics committee.

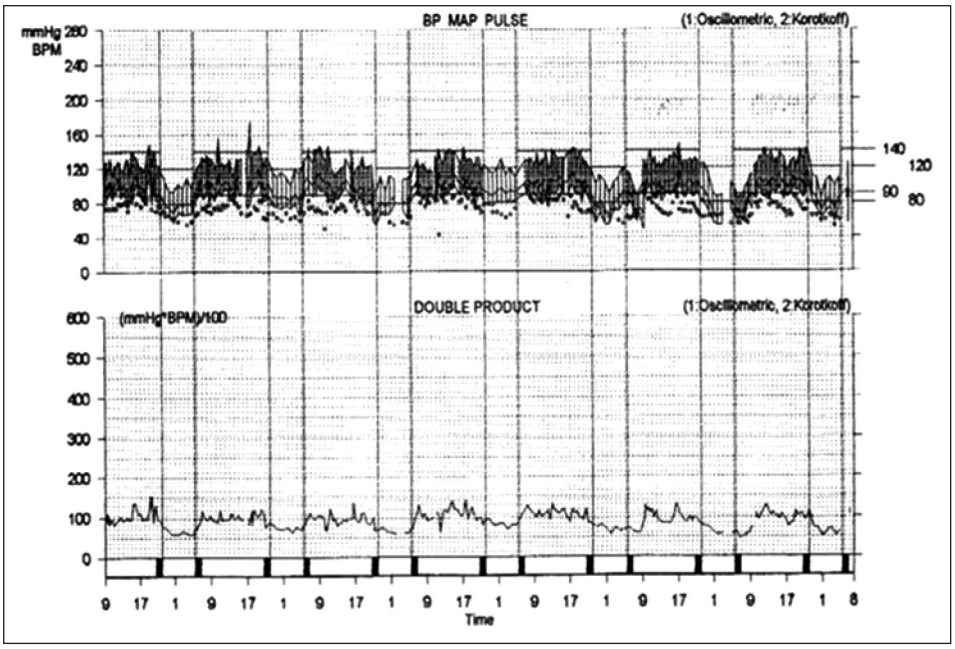

Figure 1: *Seven-day/24-h ambulatory blood pressure monitoring*

One-hour means of systolic and diastolic blood pressure were evaluated for every hour from seven-day/24-h ambulatory blood pressure monitoring.

We evaluated every day mean of 24-hour profile and 7-day mean systolic and diastolic pressure.

We analyzed day-to-day variability before and after 4 months with exercise training.

Results

In healthy subjects, the seven-day blood pressure profile (mean ± SD) in systolic blood pressure was 122±9 mmHg before the exercise training and after 4 months of exercise training it was 123±9 mmHg, as is shown in Fig. 2.

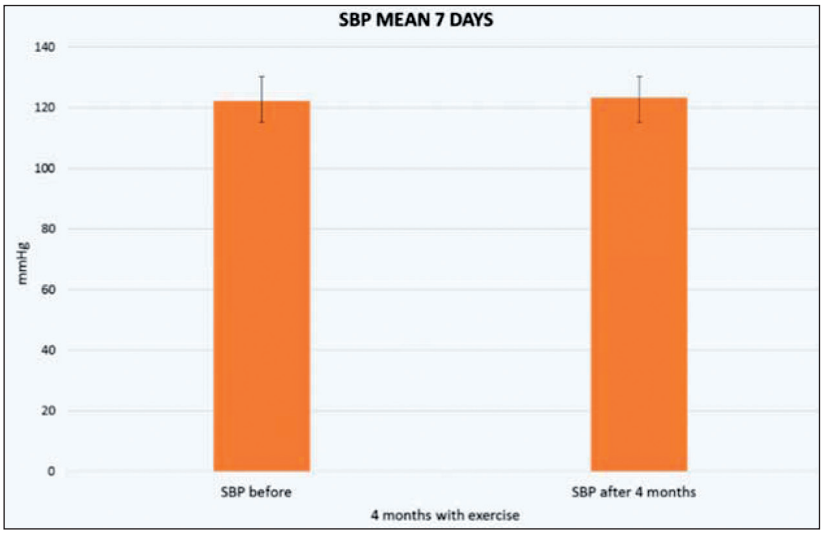

Figure 2: *Seven-day/24-h systolic blood pressure profile before and after 4 months exercise training*

In healthy subjects, the seven-day blood pressure profile (mean ± SD) in diastolic blood pressure was 70±3 mmHg before the exercise training and after exercise it was 71±3 mmHg in the whole group. These results are presented in Fig. 3.

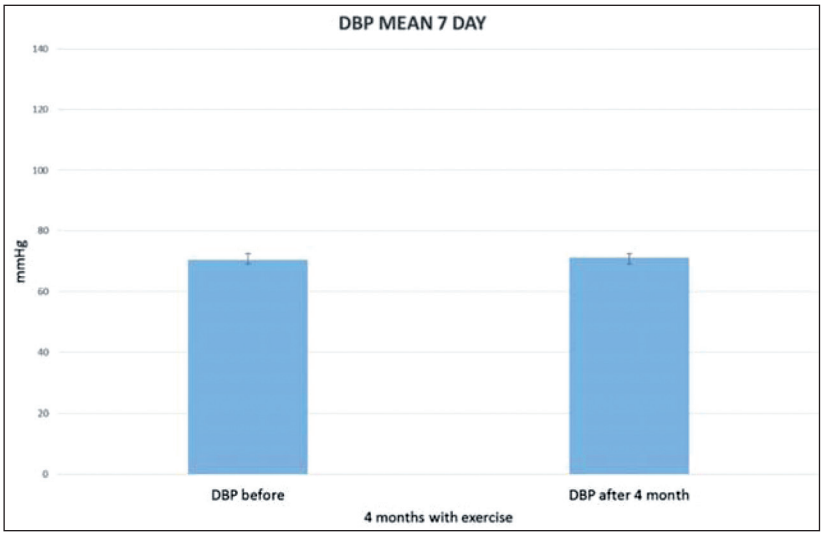

Figure 3: *Seven-day day/24-h diastolic blood pressure profile before and after 4 months exercise training*

In healthy subjects, the seven-day heart rate profile (mean ± SD) was 72.3±4.9 cycle per minute before the exercise and after exercise it was 72.9±4.8 cycle per minute in the whole group. These results are shown in Fig. 4.

Figure 4: *Seven-day day/24-h heart rate profile before and after 4 months exercise training*

Circadian variability in the following results is presented as everyday 24-h value in the black points and seven-day/24-h mean as a red line in blood pressure and heart rate.

Seven-day systolic blood pressure variability in 20 healthy subjects before exercise training is shown in Fig. 5. The lowest systolic blood pressure was 113 ± 2 mmHg, the highest systolic blood pressure 143 ± 2 mmHg.

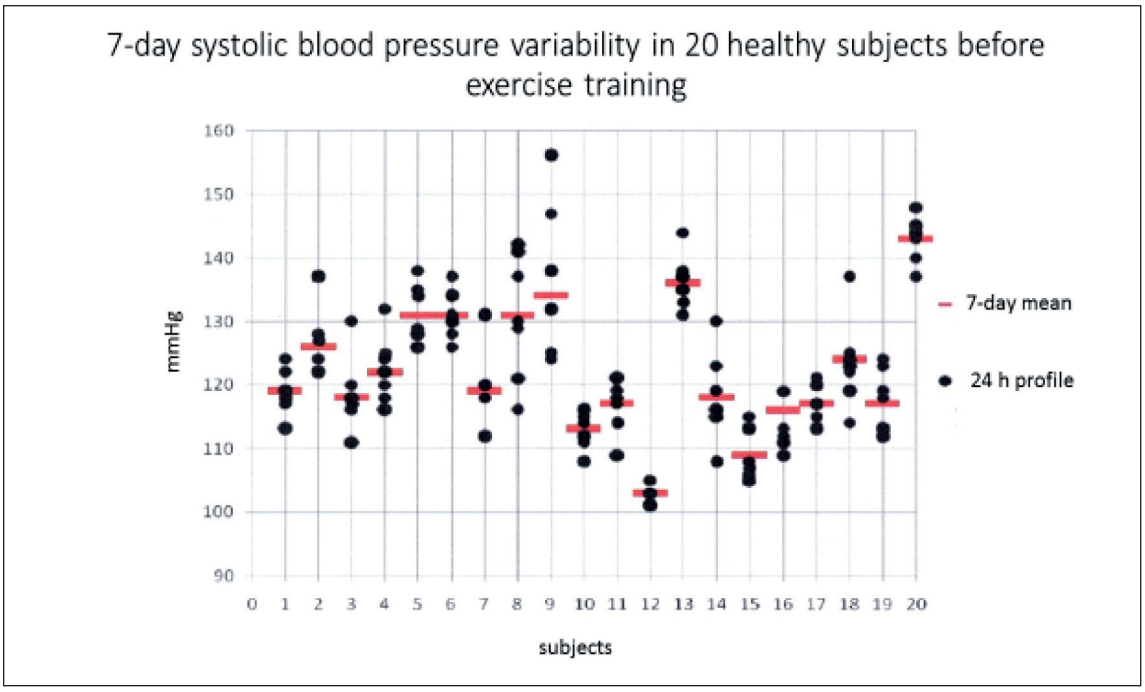

Figure 5: *Seven-day systolic blood pressure variability in 20 healthy subjects before exercise training*

Seven-day systolic blood pressure variability in 20 healthy subjects after exercise is shown in Fig. 6. The lowest systolic blood pressure was 107 ± 2 mmHg, the highest systolic blood pressure 144 ± 4 mmHg.

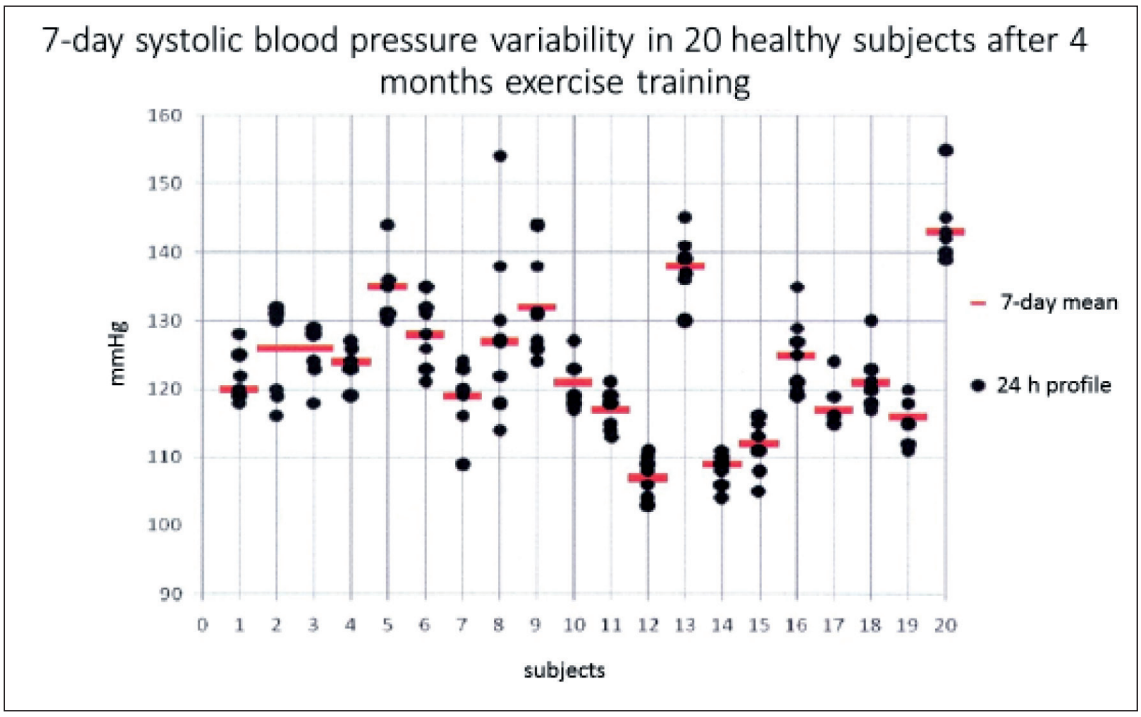

Figure 6: *Seven-day systolic blood pressure variability in 20 healthy subjects after 4 months exercise training*

Seven-day diastolic blood pressure variability in 20 healthy subjects before exercise is shown in Fig. 7. The lowest diastolic blood pressure was 64 ± 1 mmHg, the highest diastolic blood pressure 76 ± 4 mmHg.

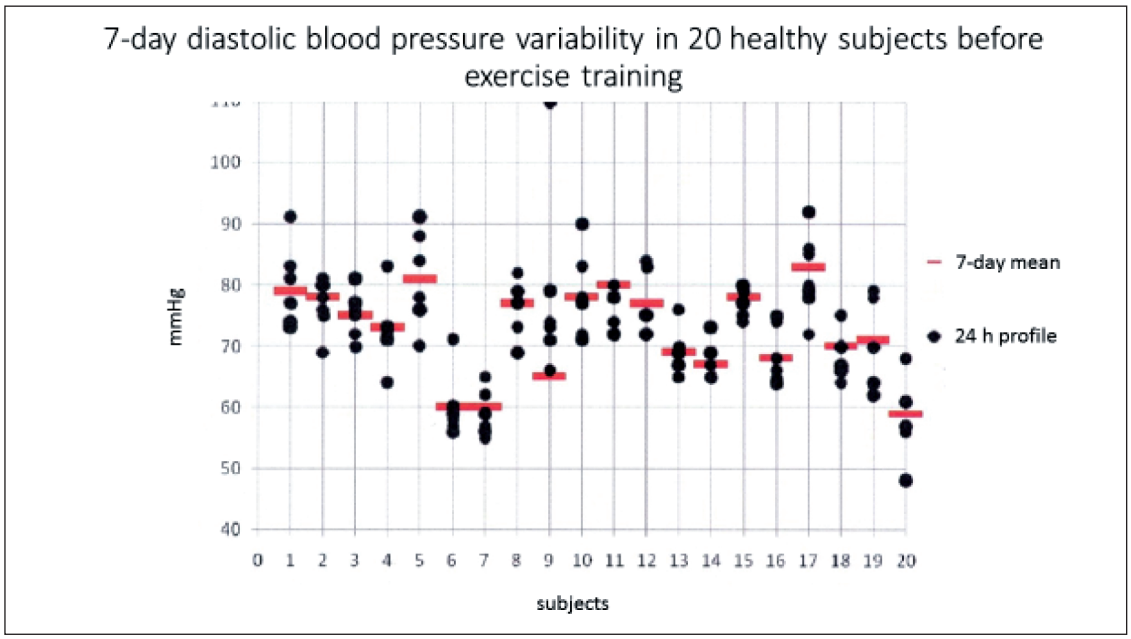

Figure 7: *Seven-day diastolic blood pressure variability in 20 healthy subjects before exercise training*

Seven-day diastolic blood pressure variability in 20 healthy subjects after 4 months exercise training is shown in Fig. 8. The lowest diastolic blood pressure was 64 ± 2 mmHg, the highest diastolic blood pressure 77 ± 3 mmHg.

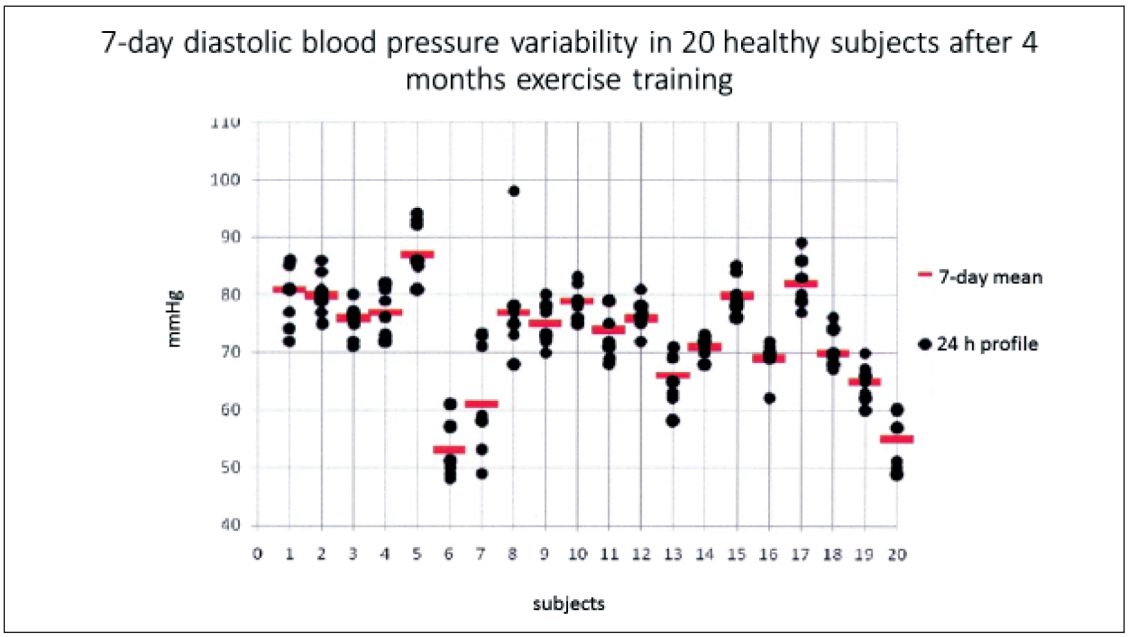

Figure 8: *Seven-day diastolic blood pressure variability in 20 healthy subjects after 4 months exercise training*

Seven-day heart rate variability in 20 healthy subjects before 4 months exercise training is shown in Fig. 9. The lowest heart rate was 58 ± 4 mmHg, the highest heart rate 80 ± 6 mmHg.

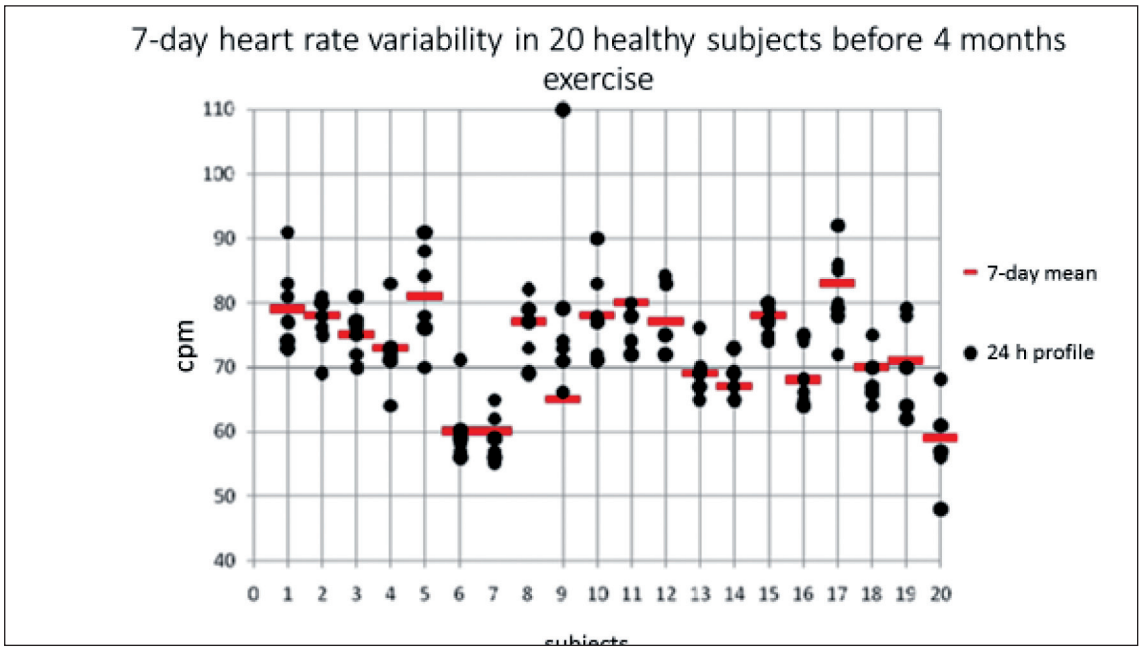

Figure 9: *Seven-day heart rate variability in 20 healthy subjects before 4 months exercise training*

Seven-day heart rate variability in 20 healthy subjects after 4 months exercise training is shown in Fig. 10. The lowest heart rate was 54 ± 4 mmHg, the highest heart rate 87 ± 5 mmHg.

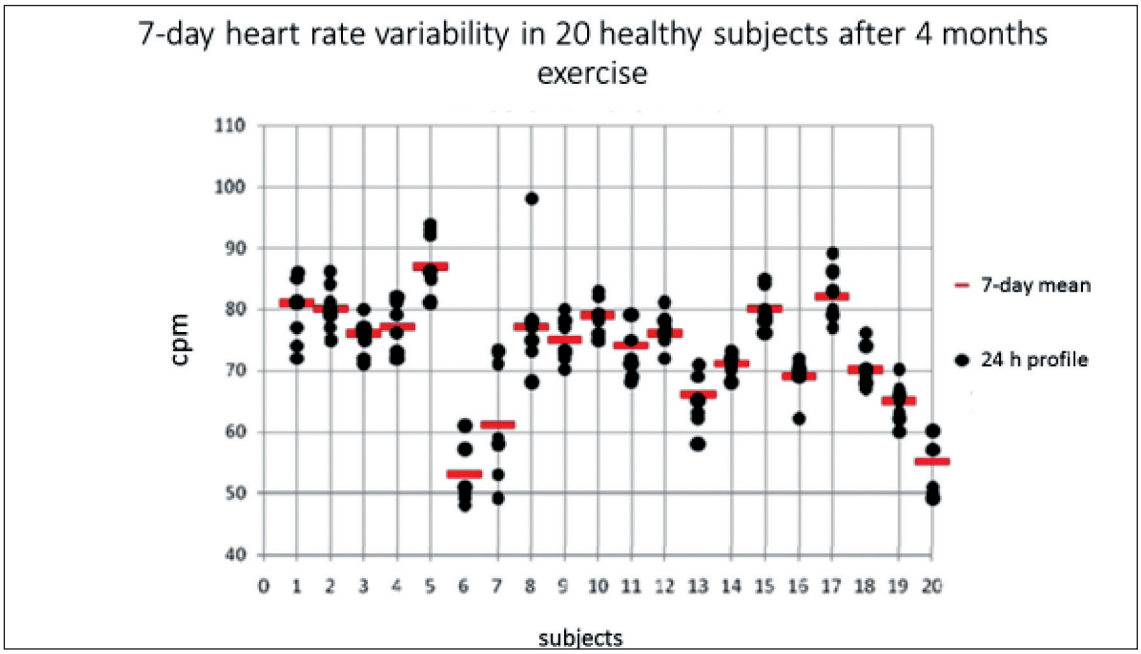

Figure 10: *Seven-day heart rate variability in 20 healthy subjects after 4 months exercise training*

24-h profile variability before and after 4 months of exercise training was present in our healthy subjects in cardiovascular parameters, measured from seven-day/24-h ambulatory blood pressure monitoring. The variability of 24-h systolic blood pressure profile was large and was present also after 4 months of exercise training. In 24-h diastolic blood pressure profile we have seen also large blood pressure variability before and after 4 months of exercise training. 24-h of heart rate also showed variability before and after exercise training. The highest and lowest values in the seven-day means are also in all subjects similar before and after training.

Discussion

Systolic and diastolic 24-h blood pressure profile varied largely and the variability of 24-h profile was not changed after 4 months of exercise training in our healthy subjects. Our previous results we have shown that in patients with increased sympathetic activity with chronic coronary artery diseases (7). The eight weeks of exercise training in patients decreased sympathetic activity and increased parasympathetic activity (8). Our results on healthy subjects in this study do not show changes in mean values of heart rate during seven-day/24-h ambulatory blood pressure monitoring. There are also differences in the age of both groups and perhaps also different living style of young students of physiotherapy and patients with chronic heart failure could play a role in our results.

Conclusion

The study showed the seven-day/24-h blood pressure monitoring before and after exercise training lasting 4 months in healthy subjects was not different. 4 months lasting exercise training, based on walking at the 70 % maximum heart rate, does not affect mean 7-day/24-h of heart rate before and after training.

Day-to-day changes of 24-h blood pressure profile systolic and diastolic blood pressure analyzed from 7-day ambulatory blood pressure monitoring, were not different before and after 4 months lasting exercise training.

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When to Exercise for Better Health

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University of Minnesota, USA

Introduction

Franz Halberg is a founder of modern chronobiology. Unlike other famous scientists devoting their activities mostly to presentation of honorary lectures at international scientific conferences Prof Halberg continued in scientific work until 2013.

The last Halberg proposal for diagnosis of vascular variability disorders on the basis of seven-day/24 hour ambulatory blood pressure and heart rate monitoring was presented in Brno Congress Noninvasive Methods in Cardiology 2008 (1, 2, 3, 4, 5).

Figure 1: *FRANZ HALBERG, M.D. Dr. h.c. (Montpellier), Dr. h.c. (Ferrara), Dr. h.c. (Tyumen), Dr. h.c. (Brno), Dr. h.c. (L´Aquila), Dr. h.c. (People´s Friendship University of Russia, Moscow), Professor of Laboratory Medicine and Pathology, Physiology, Biology, Bioengineering and Oral medicine, Halberg Chronobiology Center, University of Minnesota (*1919 - +2013)*

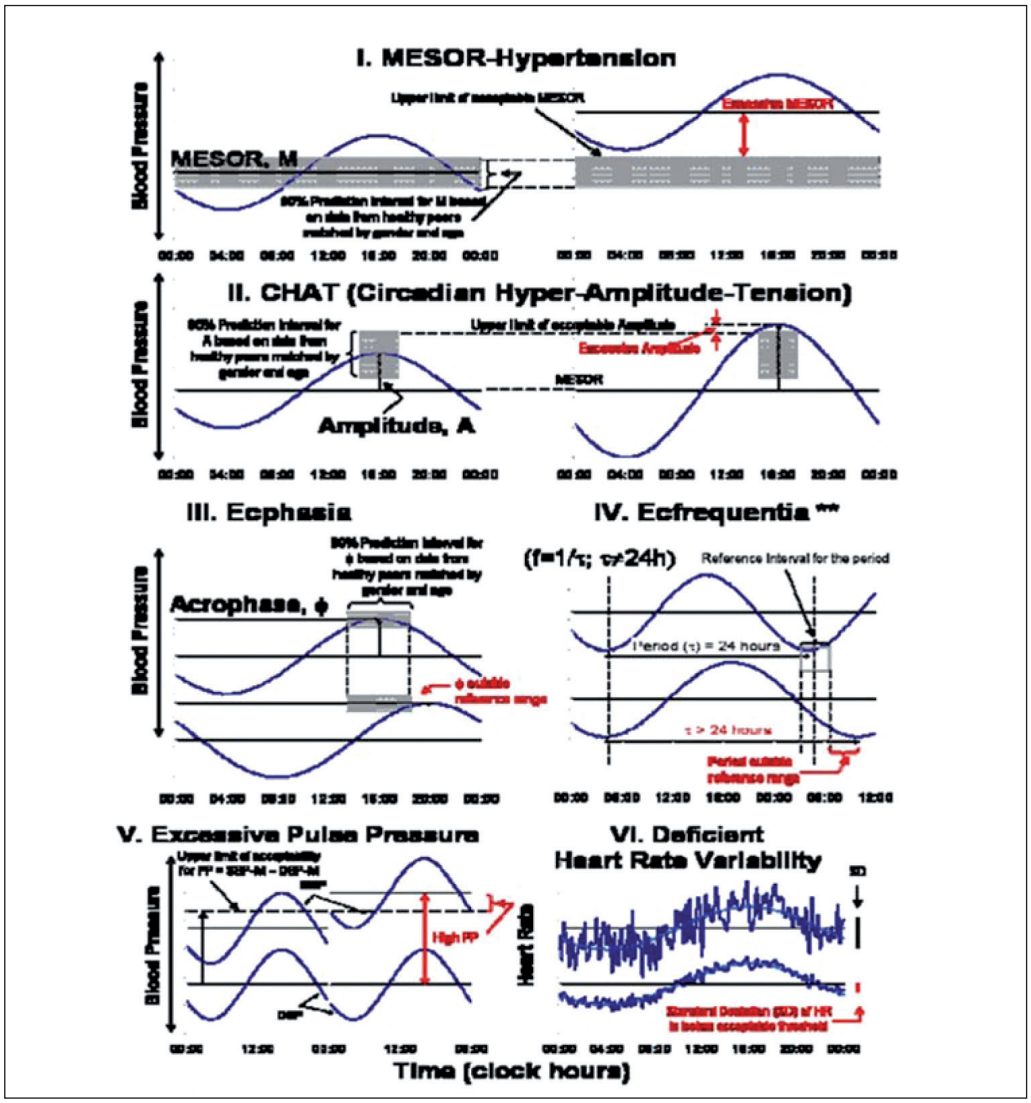

Figure 2: *Vascular Variability Anomalies (VVAs) picked up by chronobiologically interpreted 7-day around-the-clock records of blood pressure and heart rate monitoring become Vascular Variability Disorders (VVDs) when they are replicated in successive 24-hour/7-day records. If several VVDs coexist, the risk of an ischemic stroke within 6 years increases from about 5% to near 100%. To the five VVDs in the consensus, we can add a sixth, a circadian desynchronization of the endocrines and the circulation more recently documented as ecfrequentia in association with adynamia and depression recurring mostly twice-yearly in an extensively studied 62-year-old woman [10]. © Halberg*

Exercise is an easily accessible and inexpensive approach to improve cardiovascular health, control weight gain, and increase survival chances after a morbid event such as a myocardial infarction. It is, however, sometimes associated with untoward effects in vulnerable subjects. A contributory factor may be heart rate variability, which in the long-term is increased in association with exercise, but may be decreased in the short-term during exercise and the recovery span after exercise.

In cooperation with Halberg Chronobiology Center since the 1980s we have in Brno measured 658 seven-day/24 hour blood pressure profiles, which we also together analyzed with Minnesota. In cooperation we described some new findings about chronobiology of blood pressure (6, 7, 8, 9, 10, 11, 12, 13 14).

The aim of the study is to evaluate the effect of daily 1-hour exercise on the seven-day/24-hour blood pressure profile analyzed as a whole or considering each day separately.

Methods

The subjects were recruited for seven-day blood pressure monitoring. Medical Instruments (A&D, Japan) were used for ambulatory blood pressure monitoring (oscillation method). One-hour means of systolic and diastolic blood pressure were evaluated.

We calculated 24-hour mean systolic and diastolic blood pressure for seven days, then every day with exercise and every day without exercise.

We have compared the 24-hour blood pressure profile of 7 days outpatient monitoring in days with exercise (0-24 h) and in days without exercise (25-48 h) in healthy subjects and patients. We used aerobic training in 41 healthy subjects, combined training for 20 healthy people, Nordic Walking in 19 subjects and combined training in 53 patients after myocardial infarction in cardiovascular rehabilitation.

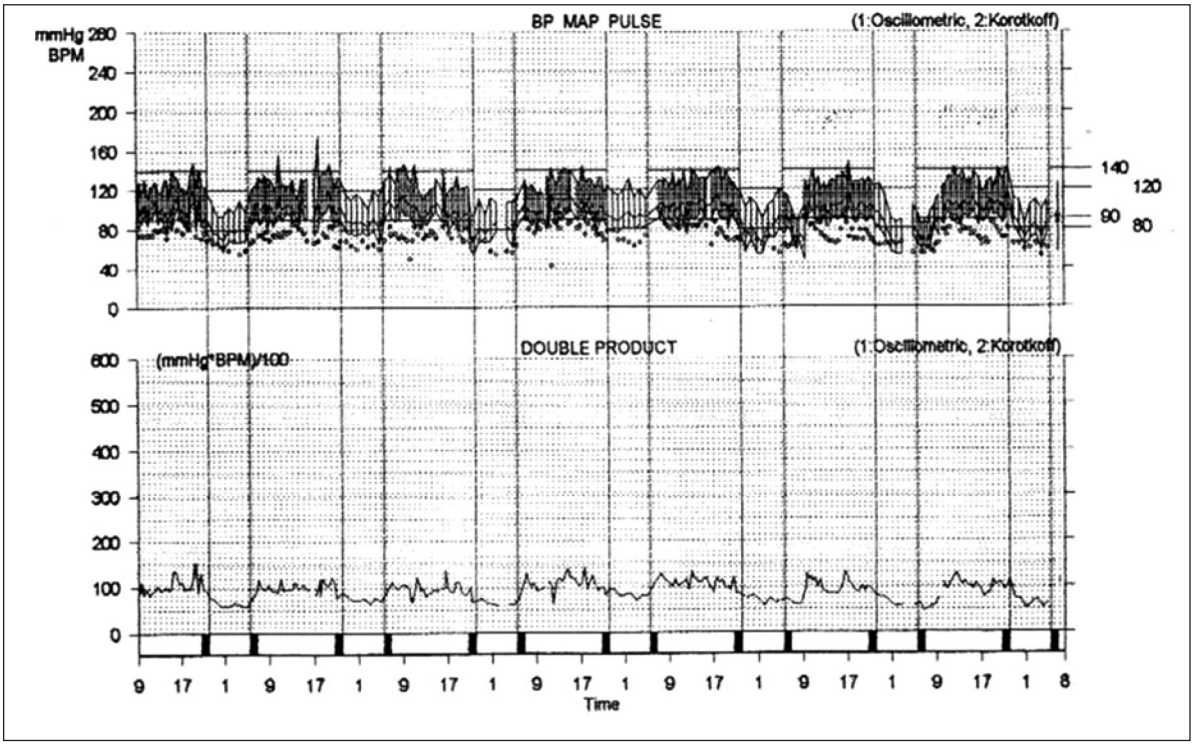

Figure 3: *Seven-day/24-h ambulatory blood pressure monitoring*

Healthy Subjects - Aerobic Training

We examined 21 men and 20 women, healthy subjects, mean age 29±4.9 years (from 23 to 39).

For exercise training we used bicycle ergometer Kettler, type X7, Germany, 2x during week, constant load 120 W in men and 80 W in women, lasting 60 min. Every exercise unit was composed from warm-up period 3 min., load 54 min. and cool-down period 3 min.

Heathy Subjects - Combined Training

We examined 5 men and 15 women, healthy subjects, mean age 29±4.9 years (from 23 to 39).

For exercise training we used aerobic and resistant training, 2x during week, constant load at the heart rate 70 % of heart rate maximum, lasting 25 min. and resistant training lasting 15 min. Every exercise unit was composed from warm-up period 10 min. and cool-down period 10 min.

Heathy Subjects - Nordic Walking

We examined 7 men and 12 women, healthy subjects, mean age 29±4.9 years (from 23 to 39).

For exercise training we used nordic walking, 2x during week, constant distance 4.3 km at the heart rate 70 % of heart rate maximum.

Patients with infarctus of myocardium

We examined 41 men and 12 women, patients with infarctus of myocardium.

The set being monitored consisted of 53 patients after myocardial infarction in the past history more than 3 months before, of mean age 63 ± 6.5 years and mean ejection fraction of the left ventricle 43 ± 12.3 %.

The patients underwent phase II of cardiovascular rehabilitation (controlled ambulatory rehabilitation program) lasting three months with the frequency of three times in a week at the Department of Sports Medicine and Rehabilitation of St. Anna Teaching Hospital.

The subjects were recruited for seven-day blood pressure monitoring. Medical Instruments (A and D, Japan) were used for ambulatory blood pressure monitoring (oscillation method). One-hour means of systolic and diastolic blood pressure were evaluated.

We calculated 24-hour mean systolic and diastolic blood pressure for seven days, every day with exercise and every day without exercise.

Results

Healthy Subjects - Aerobic Training

We compared the blood pressure profile in 24-h with exercise and in 24-h without exercise. In healthy subjects with aerobic training, seven-day/24-hour of systolic blood pressure was 115 ± 1.1 mmHg, diastolic 69 ± 1.4 mmHg, in days with exercise (0-24h) systolic blood pressure was 115 ± 2.8 mmHg, diastolic 69 ± 1.7 mmHg, in days without exercise (25-48 h) systolic blood pressure was 116 ± 3.4 mmHg, diastolic 69 ± 2.2 mmHg.

Heathy Subjects - Combined Training

In healthy subjects with combined training seven days of systolic blood pressure blood pressure was 113 ± 1.8 mmHg, diastolic 68 ± 1.4 mmHg, days with exercise (0-24h) systolic blood pressure were 112 ± 1.9 mmHg, diastolic 69 ± 1.5 mmHg, in days without exercise (25-48 h) systolic blood pressure was 113 ± 1.8 mmHg, diastolic 68 ± 1.4 mmHg.

Heathy Subjects - Nordic Walking

In healthy subjects the seven-day blood pressure mean ± SE in systolic blood pressure was 113±1.3 mmHg, in diastolic blood pressure 69±1.3 mmHg in the whole group, in the days with exercise (0-24h) systolic blood pressure was 111±1.5 mmHg, diastolic blood pressure 67±1.4 mmHg, in the days without exercise (25-48 h) systolic blood pressure was 113±1.8 mmHg, diastolic blood pressure 69±1.4 mmHg.

Patients with infarctus of myocardium

In patients with myocardial infarction, seven-day mean systolic blood pressure was 122 ± 4 mmHg, diastolic 74 ± 3 mmHg, in days with exercise (0-24h) systolic blood pressure was 121 ± 3 mmHg, diastolic 74 ± 2 mmHg, in days without exercise systolic blood pressure 121 ± 3 mmHg, diastolic 73 ± 3 mmHg.

In all healthy subjects and patients our results showed that 1-hour of aerobic training and combined training did not change the 24-hour MESOR of systolic and diastolic blood pressure profile, assessed from a seven-day ambulatory blood pressure monitoring (7 days / 24 hours) in healthy subjects and in patients.

Timing of exercise

Exercise training should be timed according to the circadian blood pressure profile before starting the program. If the circadian blood pressure amplitude is excessive, we have found that it is preferable to time exercise earlier in the day (from 7:30 to 19:00) since evening exercise may increase the circadian amplitude of blood pressure and thus potentially cause harm (16). Ambulatory monitoring interpreted chronobiologically can serve for the optimization of the timing of exercise on an individual basis.

Discussion

In our earlier study we asked what is the best time of exercise (16). As part of a healthy lifestyle or for rehabilitation purposes, exercise is currently practiced at times of convenience rather than pertinence. To examine whether the timing of exercise can be optimized on an individual basis, a 68-year old man measured his blood pressure and heart rate around the clock at 30-min intervals with an ambulatory monitor (TM-2421, A&D, Tokyo, Japan), for spans of 4-7 days. He exercised at different times (around 06:00, 09:00, 12:00, 15:30, and 18:00). Each day's data as well as each record as a whole was analyzed by cosinor to obtain estimates of the MESOR (M, rhythm-adjusted mean), and 24-hour amplitude and acrophase (phase of fitted model's maximum) (3). Results were assigned to the clock hour of exercise during the given span to yield new time series amenable to cosinor analysis (3), complementing the one-way analysis of variance, the main effect being timing of exercise.

The immediate response of blood pressure and heart rate to graded exercise was also circadian stage-dependent in an earlier study on four marathon runners. The smallest blood pressure response occurred around mid-day, larger decreases observed when exercise was done earlier or later in the day (15). Exercise by a 46-year old man was associated with an increase in the circadian amplitude of blood pressure that was more pronounced when exercise was done in the evening than in the morning, in his case leading to an abnormal circadian pattern potentially carrying an increased cardiovascular disease risk, as recorded by us (2).

Depending on whether the circadian pattern of blood pressure at the outset tends to have too large an amplitude or not, exercise should be timed to reduce both long-term and short-term blood pressure without bringing about an abnormal variability in blood pressure that may be harmful. Ambulatory monitoring interpreted chronobiologically can serve for the optimization of the timing of exercise on an individual basis.

Conclusion I

In this study we also analyzed the timing of exercise. One of our studies showed that the exercise at 9 o´clock in the evening increases the Circadian Hyper-Amplitude Tension (CHAT).

Our studies showed that the exercise in the daily time between 7:30 until 19:00 h does not evoke the Circadian Hyper-Amplitude Tension (CHAT) in healthy subjects and in patients.

Conclusion II

From the results we can conclude that 24-hour blood pressure MESOR at rest and during exercise from day-to-day vary in healthy subjects as well as in patients with coronary heart disease IM were not different in the days with the exercise and without exercise.

The healthy subjects during different kinds of exercise activity get the similar results in 24 h blood pressure profiles in comparison with the days without exercise.

On the basis of our results we recommend the 7-day blood pressure monitoring or home blood pressure monitoring. The education for long-lasting self-monitoring is the best approach for management of hypertension.

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Ambulatory Rehabilitation Program for Patients with Cardiovascular Diseases

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Introduction

Cardiovascular diseases (CVD) are still the leading cause of death in Europe (4.4 million deaths/ year, that is, 48% of all deaths yearly). The formidable development and investment in high-technology diagnostic and therapeutic procedures for cardiovascular diseases (CVD) in past decades increased survival. Age-adjusted mortality rates have decreased considerably in many European countries, that is, people are living longer with heart disease. The actual challenge is an optimization of the disability-free survival including active participation in social and economic life for patients after cardiovascular events. However, resulting benefit is not automatically achieved through HI-TECH interventions and pharmacotherapy alone but also through cardiovascular rehabilitation (CV-RHB) programs. AHA and AACVPR define CV-RHB programs as: ***„Coordinated, multifaceted interventions designed to optimize a cardiac patient's physical, psychological, and social functioning, in addition to stabilizing, slowing, or even reversing the progression of the underlying atherosclerotic processes, thereby reducing morbidity and mortality„*** (1).

A CV-RHB program is tailored to the individual needs and health condition of the patient and the rehabilitation professional staff should set the exercise program according to the specific health situation and goals (2, 3 and 4). Most cardiac rehabilitation programs in the Czech Republic last about 8 to 12 weeks. During that time, the patient may work with cardiologists, nurse educators, dietitians, physiotherapists specialized in cardiovascular rehabilitation and psychologists.

CV-RHB classification

Current classification of CV-RHB has 4 main phases: Phase I (in-hospital); Phase II (outpatient) which can be provided as a) ambulatory supervised program; b) spa treatment; and c) individual home training. The remaining two phases are Phase III (stabilization period) and Phase IV (maintenance period).

Phase I (early; in-hospital)

Ideally, the cardiac rehabilitation program starts while the patient is still in hospital. The duration of this phase may vary depending on the initial diagnosis, the severity of the event and individual medical institutions. CV-RHB program begins with non-strenuous activities, such as sitting up in bed, range-of-motion exercises and self-care, such as shaving. Then, the patients can progress to walking and limited stair climbing. They can engage in the kinds of activities they will encounter once back at home.

Phase II (outpatient; early recovery)

This phase of cardiac rehabilitation begins when the patient leaves the hospital and is often done in a rehabilitation center. Most cardiac rehabilitation programs of Phase II in the Czech Republic generally last about 8 to 12 weeks. During this phase, the patient gradually increases his activity level under the close supervision of cardiac rehabilitation team. The CV-RHB team might suggest exercises which can be safely do at home, such as walking, gentle calisthenics. The patient can also learn about eating a healthy diet, quitting smoking, coping with health condition, resuming sexual activity and finding social support. If the patient doesn't have a nearby medical facility with a cardiac rehabilitation center, the CV-RHB team can advise him about safe training at home. In the Czech Republic, the Public health insurance covers fully the costs of cardiac rehabilitation Phase I and II.

Phase III and IV (ongoing recovery and maintenance)

This is a long-term maintenance program — something to follow for the rest of patient´s life. By this point, the patient probably will have developed his own exercise routine at home or at a local gym. The patient may also continue to exercise at a cardiac rehabilitation center. The patient may remain under medical supervision during this time, particularly if he has special health concerns. Education about nutrition, lifestyle and weight loss may continue, as well as counseling. For best success, it is necessary to make sure the exercise and lifestyle practices become patient´s lifelong habits.

Indications and contraindications

Generally, the CV-RHB is indicated for all patients with the following diagnoses: coronary interventions (PCI), coronary revascularization (coronary artery bypass graft), cardiac surgery (valvular, transplantation, congenital heart diseases), chronic stable AP, acute myocardial infarction (AMI), heart failure, peripheral artery disease (PAD), and high-risk patients for cardiovascular disease (diabetes, metabolic syndrome). The main contraindications for inclusion into the CV-RHB program are: sinusal tachycardia (>120 bpm), systolic blood pressure (SBP >200 mmHg), diastolic blood pressure (DBP >115 mmHg), symptomatic hypotension, acute infection, heavy aortic stenosis, dissecting aneurysm of the aorta, unstable AP, acute heart failure, suspected pulmonary embolism, and ventricular tachycardia or life-threatening arrhythmias (2).

CV-RHB program of Phase II

Time to start the CV-RHB program Phase II is within 3 weeks after acute coronary event („as soon as possible"), and within 6 weeks after cardiosurgery or intervention (until then, walking and scar care is recommended). Resistance training can be included only three months after intervention. Inclusion in the outpatient CV-RHB program (Phase II) is submitted by cardiologist, internist, or general practitioner. Before starting the CV-RHB, all patients are examined by a cardiologist who controls them also in the whole course of the program. Before inclusion into the CV-RHB program, all patients undergo a spiroergometric test to assess functional capacity and training intensity (4). Spiroergometric test (Power Cube, Ganshorn® Medizin Electronic, Niederlauer, Germany) is done using an incremental ramp exercise protocol on bicycle ergometer (Ergoselect 200, Ergoline®, Bitz, Germany). Twelve-lead ECG is monitored continuously (AT-104 PC, Schiller®, Baar, Switzerland). Patients are instructed to maintain a stable RPM (60 rev.min^{-1}) and the workload is automatically increased gradually from 0 to the tolerated maximum (W.min^{-1}). HR is continuously and automatically recorded during the test, and BP is measured manually every 2 min. Standard ventilation and respiratory gas exchange parameters

(VO_2, VCO_2, ventilation – VE) are measured using the "breath by breath" method, peak oxygen uptake (VO_{2peak}) is expressed as the highest value of O_2 reached in the last 30 s of exercise. Peak HR (HR_{peak}) and peak workload (W_{peak}) are determined in the same way. Ventilatory anaerobic threshold (VAT-1) is determined by a standard method according to Wasserman (5). An identical protocol for the spiroergometric test is also realized after completion of the CV-RHB program.

Training session of the ambulatory CV-RHB program

Structure of the training session during the first 2 weeks of CV-RHB program includes the „warm-up" period (10 min), aerobic endurance training on bicycle ergometers (40 min), and relaxation or „cool-down" period (10min). Total time of one session is 60min. The training is done 3x/week as a group exercise (standard duration of the whole CV-RHB program is 12 weeks). After the first 2 weeks of CV-RHB program, a resistance training is added and the structure of the training session is as follows: „warm-up" period (10 min), aerobic training on bicycle ergometers (25 min), resistance training (15min) and „cool-down" period (10min) for total time 60min. This type of training is called „combined", and is applied during the 3rd – 12th week of CV-RHB program. HR and BP at rest are measured regularly before the beginning of the training session (BP manually using manometer, and HR continuously by wearable system Polar-Tester).

„Warm-up" period of the CV-RHB training session consists of simple exercises (including gymnastic tools) and dynamic stretching exercises, aiming to warm-up the body and muscle mass. The „warm-up" period takes place with a musical accompaniment under the guidance of a physiotherapist. Aerobic (endurance) training on bicycle ergometers is automatically driven using software Ergosoft 2 (Ergoline® Co., Germany) which enables accurate setting of the training type, its intensity and the continual recording of ECG curves (Fig. 1).

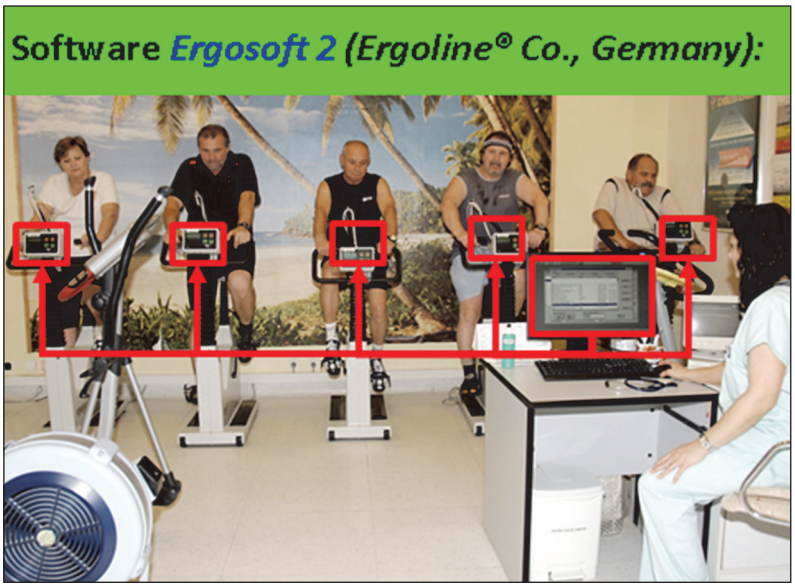

Figure 1: *Aerobic endurance training on bicycle ergometers with software Ergosoft 2 (Dept. of Sports Medicine and Rehabilitation, St.Anne´s Faculty Hospital Brno)*

HR, BP and RPE are monitored during the whole training session. During the period of aerobic (and resistance) training it is necessary to watch carefully any signs of poor exercise tolerance (excessive dyspnea, stenocardia), significant overshoot of training HR, episodes of bradycardia or arrhythmias, vertigo, collapse state, etc. Two basic variants of aerobic endurance training are provided

to the patients included in the CV-RHB program: a) aerobic continuous endurance training (CT) with constant workload interval training (IT); and, b) aerobic endurance training with variable intensity (″on-off″ mode). CT is applied with workload intensity at the level of the ventilatory anaerobic threshold (VAT-1) determined by the spiroergometric test. IT is applied at the beginning of CV-RHB program or permanently in low-tolerance patients (IT is less demanding than continuous). IT consists from 30-sec workload (intensity at the level of VAT-1) which is alternated with a 60-sec relaxation phase (50% of workload at VAT-1). Resistance training is realized using special multifunctional fitness system Tendo HC COMPACT® (Czech Republic). One-repetition maximum test (1-RM) in weight (resistance) training is the maximum amount of force that can be generated in one maximal contraction. The result of this test (for each exercise) is used to determine the training workload at the level of 30%, 40%, 50%, and 60% of 1-RM. The resistance training consists of a variety of specific exercises, such as bench-press in sitting position, leg extension, pull-down the pulley in sitting position, pull-down the pulley in standing position, etc. „Cool-down“ or relaxation phase typically includes low-intensity exercises, slow walking, static stretching, special relaxation techniques and also Schultz autogenic training (10 min). The purpose of the outpatient CV-RHB program is not only to improve the fitness, but also to motivate the patient to adopt a healthy lifestyle based on regular physical activity, proper nutrition, mental well-being and permanent smoking cessation. Counseling for smoking cessation is provided by the staff of Central Pharmacy (St. Anne´s Faculty Hospital, Brno). Counseling for a healthy diet is provided by a nutritionist (Department of Sports Medicine and Rehabilitation, St. Anne´s Faculty Hospital, Brno). CV-RHB program of the Phase II and III, provided by the Dept. of Sports Medicine and Rehabilitation (St. Anne´s Faculty Hospital, Brno), was founded in 1998 by Professor Jarmila Siegelova, in close cooperation with the Swiss Cardiovascular Center in Bern (Switzerland), led by Professor Hugo Saner.

Conclusion

Adjusting to a serious health problem often takes time. Cardiac patients may feel depressed or anxious, lose touch with their social support system, or have to stop working for several weeks. If they get depressed, they should not ignore it, because depression can make the CV-RHB program more difficult, as well as negatively influence the relationships and other areas of patients´ life and health. Counseling provided by health professionals could help to learn healthy ways to cope with depression and other feelings, and may also suggest medications such as antidepressants. Vocational or occupational therapy can promote new skills to help the return to work. One of the most valuable benefits of cardiac rehabilitation is often an improvement in the quality of life, both physical and emotional. As the patient gets stronger and learns how to manage the health condition he can likely return to a normal routine and enjoy life more. It is important to know that the chances of having a successful cardiac rehabilitation program rests largely on the patient – the more dedicated he/she is to following the program's recommendations, the better he/she will do. Up until the 1970s, strict bed rest was thought to be the best medicine after an acute cardiac event. Following discharge moderately stressful activity such as climbing stairs was discouraged for a year or more. Dr. Thomas LEWIS (1881 – 1945), an outstanding British cardiologist, wrote: „The patient is to be guarded by day and night nursing and helped in every way to avoid voluntary movement or effort“. Dr. Lewis was the author of the monograph "Diseases of the Heart" (1932) which was a medical bestseller at the time. Today, CV-RHB program is regarded as a lifelong multidisciplinary approach which combines exercise training, risk factor modification, medical surveillance, emergency support, and psychological and vocational counseling. And what will be the patient´s main outcome of cardiovascular rehabilitation in the long run? Although it may be sometimes quite difficult to start a cardiac rehabilitation program when the patient does not feel well, he/she will benefit in the long run. Cardiac rehabilitation can

guide him through fear and anxiety as he/she returns to an active lifestyle, with more motivation and energy to do the things he/she enjoys. Over the long term, he will gain strength, learn heart-healthy behaviors, improve his/her diet, cut bad habits such as smoking, and learn how to cope with heart disease. Although studies show the CV-RHB program can improve the quality of life and help to live longer, many people are not even aware about. And despite the above-mentioned numerous benefits, the role of physical activity is still underestimated and physical hypo- or inactivity remains highly prevalent worldwide (6).

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Effect of Cv-Rhb Program on Main Functional Parameters and Arterial Stiffness in Patients with Cardiovascular Diseases

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Introduction

Regular exercise and diet habits are well-known determinants of the extent of arterial stiffening in healthy aging (1 and 2). Both these lifestyle measures represent clinically valuable interventions to improve arterial biomechanical properties beyond their impact on blood pressure (BP) and other conventional risk factors (3). The association of aortic and proximal arterial stiffness with cardiovascular and all-cause mortality is independent of conventional risk factors and strongest in the setting of higher cardiovascular risk (4). Aerobic exercise has been attractive for reducing arterial stiffness since the demonstration of improved systemic arterial compliance and aortic β-stiffness index in healthy, sedentary young adults (5). Moreover, arterial properties after training were similar to those in endurance athletes in spite of a relatively modest exercise dose (cycling 3 × 30 min per week at 75% of maximum workload; 6). These short-term changes may argue for exercise-mediated arterial adaptations being predominantly functional rather than structural in origin (7).

Patients and methods

Until now, we evaluated a group of patients with CAD (n = 171; 135 men, 36 women, mean age 65 ± 11.7 yrs and mean EF 48.4 ± 12.4%). Forty two patients have hypertension, 120 dyslipidemia, 49 diabetes mellitus, 33 chronic heart failure (NYHA I-III), 19 valvular disease, and two patients were transplanted. As mentioned above, a standard spiroergometric test („breath by breath“ analyzer Power Cube, Ganshorn® Medizin Electronic, Niederlauer, Germany; 12-lead ECG monitoring by AT-104 PC, Schiller®, Baar, Switzerland) on electromagnetically braked bike ergometer Ergoselect, Ergoline®, Bitz, Germany) was performed at baseline in all patients included in Phase II for assessment of peak oxygen uptake ($VO_{2\ peak}$), ventilatory anaerobic threshold (VT-1), peak workload (Wpeak) and peak heart rate (HR_{peak}) for determination of the functional capacity and training intensity setting. Arterial stiffness was assessed by the cardio-ankle vascular index (CAVI) and measured by VaSera® 1500 (Fukuda Denshi Co, Tokyo, Japan) using a standard protocol described previously (8). Patients with an ankle-brachial index (ABI) of less than 0.9 were excluded from this study.

Ethics

All the patients included have signed the “Patient´s Informed Consent”. The study was approved by the local ethics committee and corresponds to the principles of the Helsinki Declaration (revised in 2013) and the GCP guidelines of the European Community.

Statistics

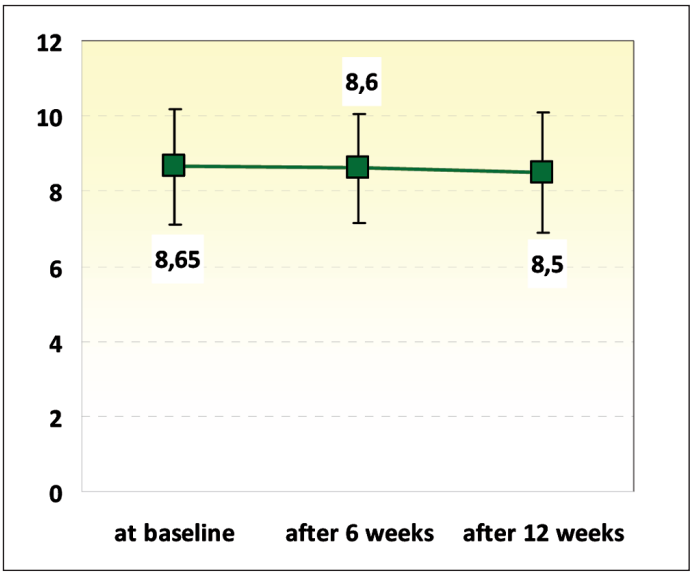
Standard descriptive statistics was applied in the analysis: a) continuous variables: mean with 95% confidence interval (CI) or standard deviation (SD) and median with 5th and 95th percentile; and, b) categorical variables: absolute and relative frequencies. Statistical significance of CAVI changes in time between admission and 6th week or 12th week was tested using paired t – test. All statistical analyses were computed using SPSS 19.0.1 (IBM Corporation, 2010). A value $p < 0.05$ was accepted as boundary of statistical significance in all applied tests.

Results

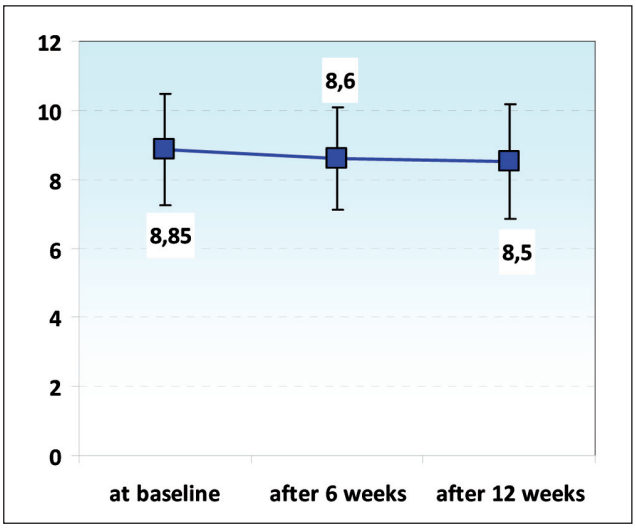
Table 1 summarizes the results of main functional variables. Twelve weeks of supervised exercise training significantly improved the aero-metabolic capacity (expressed as VO_{2peak}) and also the peak workload. These findings are consistent with the previously published conclusions that purposeful exercise in patients with CAD improves exercise tolerance and habitual activity and should be considered as important lifestyle component. Supervised CV-RHB program resulted in a significant decline of mean value of the parameter CAVI after 6 weeks from 8.65 ±1.55 to 8.6 ± 1.47 ($P<0.05$), and to 8.5 ± 1.61 ($P<0.01$) after 12 weeks (Graph 1). Similarly, a prominent decrease of mean CAVI was observed in the group of men (n = 135): from 8.85 ± 1.61 to 8.60 ± 1.48 ($P<0.01$), and to 8.50 ± 1.67 ($P<0.01$) at the end of CV-RHB program (Graph 2). The mean CAVI value in the group of women (n = 36) declined after 6 weeks of exercise training from 8.60 ± 1.30 to 8.5 ±1.42, but the reducing trend did not show a significant change ($P< 0.061$). Nevertheless, after the completion of 12-weeks CV-RHB, the decrease of mean CAVI in this group was statistically significant (8.4 ±1.34; $P<0.01$; Graph 3). It is likely that the non-significant decline of CAVI after 6 weeks of exercise training was influenced by lower number of female patients included.

Parameter:	At baseline:	After 12 weeks of CV-RHB :	p*
peak oxygen uptake *(ml . kg⁻¹)*	19.3 ± 6.2	21.5 ± 5.6	0.003
peak workload *(W . kg⁻¹)*	1.43 ± 0.4	1.67 ± 0.6	0.02
RER	1.12 ± 0.07	1.14 ± 0.08	NS
peak heart rate *(bpm)*	122 ± 31.3	135 ± 27.7	NS

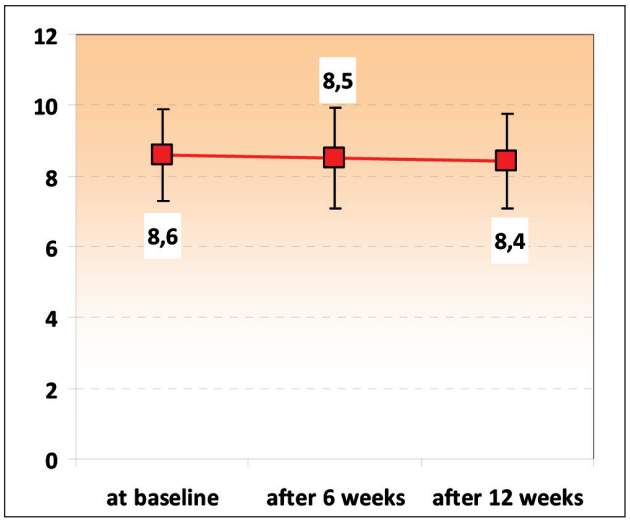
Table 1: *Results of main functional parameters*



Graph 1: *Time-course of CAVI changes at baseline, after 6 and 12 weeks of CV-RHB (whole group; n = 171)*



Graph 2: *Time-course of CAVI changes at baseline, after 6 and 12 weeks of CV-RHB (group men; n = 135)*



Graph 3: *Time-course of CAVI changes at baseline, after 6 and 12 weeks of CV-RHB (group women; n = 36)*

The applied training protocol was well tolerated by all the patients included in the study. No abnormalities or life-threatening events were observed during the training period. There was no evidence of severe arrhythmias, and pathologic changes of HR or blood pressure.

Discussion

Parameter CAVI is strongly associated with the presence and severity of coronary atherosclerosis and is considered as useful predictor of coronary atherosclerosis in subjects with a risk factor for cardiovascular disease (9). The obtained results confirmed our previously published data that regular supervised CV-RHB program can promote a significant drop in arterial stiffness (10). Also in this study the parameter CAVI has been shown to be a valuable diagnostic tool for precise monitoring of adaptive vascular changes induced by long-term physical activity leading to reduced peripheral resistance. The main mechanisms involved in vascular smooth muscle cell regulation include arterial wall shear stress, nitric oxide production, vasomotor tone, oxidative stress and inflammation (11). Even it seems that vascular functional adaptations following physical activity are independent of traditional risk factors, concurrent BP drop may contribute to early de-stiffening (Figure 1).

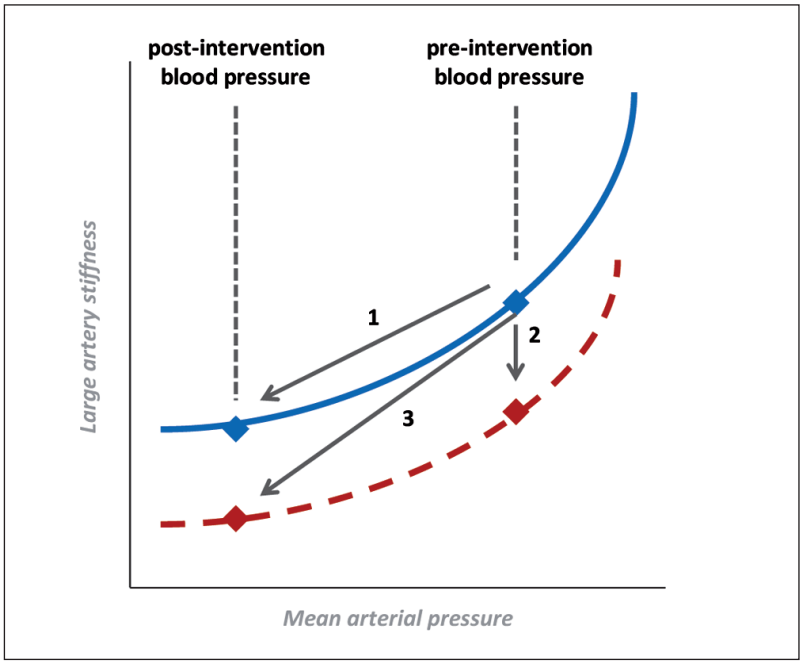


Figure 1: *Mean arterial pressure–stiffness curves demonstrate the biomechanical implications of arterial functional vs. structural responses to aerobic exercise training. (1) Functional de-stiffening: Lower mean arterial pressure translates to a reduction in stiffness by virtue of a shift in the curve's operating point. (2) Structural de-stiffening: A reduction in intrinsic stiffness of the arterial wall manifests in a downward shift of the entire pressure-stiffness curve (dashed line). Reduced stiffness is evident for a given mean arterial pressure. (3) Functional + structural de-stiffening: Combination of (1) and (2). Scheme modified (12)*

Animal experiments proved long-term structural vascular adaptations by exercise training but still remain difficult to demonstrate in humans (7). Increased arterial stiffness present in CAD may have important implications for exercise capacity because it may determine the ischemic threshold independent of stenosis severity (13). Physical activity such as endurance aerobic training can improve endothelial dysfunction and arterial stiffness as well as myocardial perfusion in patients with CAD. However, (14) in a detailed review article reported that the information about the effects of training programs on AS in patients with CAD is still very rare (14). Thus, the generally observed reduction of AS after exercise training is based only on a small number of studies. Moderate-intensity resistance

training seems to have a neutral effect on arterial properties in healthy individuals but given its possible benefits for cardio-metabolic risk reduction (including BP lowering), further studies are needed in populations with cardiovascular and metabolic diseases (15 and 16). Since exercise and dietary interventions may reduce arterial stiffness by a variety of mechanisms, additive effects on arterial stiffness are possible, but evidence is scarce. The present gold-standard lifestyle intervention could arguably be based on the most successful interventions, such as regular aerobic exercise, healthy diet habits, and body weight reduction. Although this combination should markedly reduce arterial stiffness, poor adherence is a major drawback to intensive lifestyle modification. It must also be acknowledged that even if it is possible to modify arterial properties non-pharmacologically, it is still unclear whether this will translate to improved prognosis. However, given its fundamental importance to arterial–ventricular coupling and cardiovascular function (Figure 2), the reduction of arterial stiffness is crucially important and a challenge for future research. These observations suggest that physical exercise is an effective, inexpensive lifestyle strategy for regeneration and stabilization of the vascular system, which otherwise decreases with age and chronic vascular diseases.

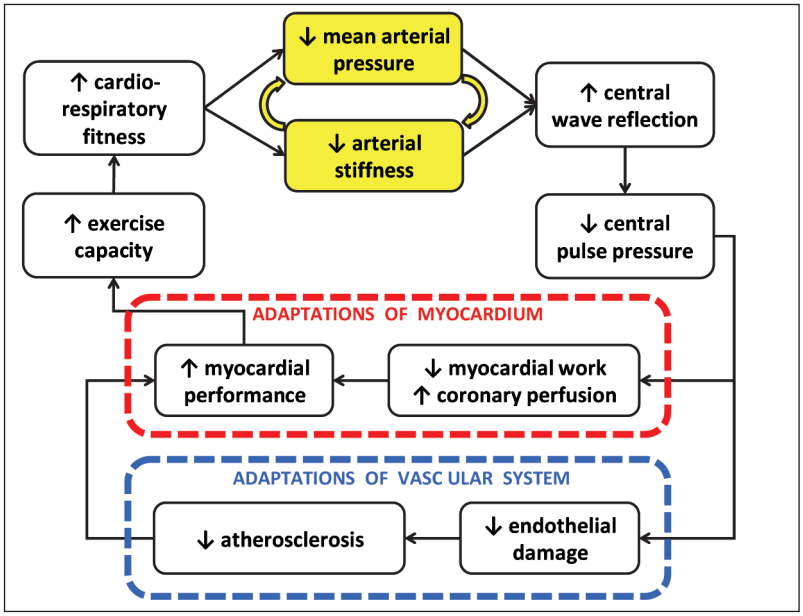


Figure 2: *Virtuous cycle by which enhancement of cardio-respiratory fitness and arterial de-stiffening may promote each other. Improved fitness is associated with reductions in both arterial stiffness and blood pressure, which not only lower central wave reflection and pulse pressure (in turn) but may also promote each other within their own virtuous sub-cycle. Reduction in pulse pressure has distinct cardiac and vascular effects, the former including a decrease in myocardial afterload coupled with enhanced coronary blood flow, and the latter facilitating less endothelial damage and curtailing of atherosclerotic burden. These collective cardiovascular adaptations serve to increase myocardial performance, a key determinant of exercise capacity (cardiorespiratory performance) in patients with cardiovascular diseases. Scheme modified (13).*

Conclusion

In conclusion, the supervised CV-RHB program applied in this study reduced significantly mean AS in patients with CAD. Our study is very likely the first attempt to evaluate the effects of exercise training program on arterial stiffness in patients with CD using the parameter CAVI (all published trials evaluated AS by PWV, arterial augmentation index, etc. but no CAVI).

Acknowledgement

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CATkit: A Toolkit for Chronobiological Study with Diverse Applications

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The study of biological rhythms is a rapidly growing area of study. Flexible, comprehensive tools are key to successful research outcomes. A new tool is available to chronobiology researchers. CATkit is freely available on CRAN, the Comprehensive R Archive Network, a repository of R packages.

As shown in Figure 1, CATkit includes both visualization tools and tools for quantitative analyses. It has been used around the world for an array of applications and subject areas. The Halberg Chronobiology Center received inquiries about CATkit from researchers at Universities across the US, in India, United Kingdom, Norway, Scotland, The Netherlands, Turkey, Brazil, France and Germany in biological, sociological, psychiatric, medical, computing and pharmacological subject areas (Lee Gierke and Cornelissen, 2016).

Collaborations with CATkit

Chronobiology impacts can be seen across scientific domains. Here are a few of the people we have worked with.

A colleague at the Experimental and Systems Pharmacology College of Pharmacy, Washington State University, analyzed qRTPCR data using the cosinor analysis in CATkit. Data contained expression profiles of 7 patients measured at 2, 5, 8, 11, 14, 17, 20 and 23 hours. Using this gene expression data, they made comparisons between two classes of patients (day shift vs. night shift). Data were collected from approximately 750 genes. Cosinor analysis is being used to investigate whether rhythms need to be modelled by single- or multiple-components, and what are their respective periods.

The Halberg Chronobiology Center worked with these researchers to determine whether their data were adequate for qualitative analysis tools, as well as methodologies and program parameterization.

Researchers at the Department of Digestive Diseases at Rush University Medical Center, in Chicago, IL, have been studying multiple aspects of circadian misalignment in GI health. A recent project was on the impact of night shift work on alcohol-induced intestinal permeability, which is a marker for alcoholic liver disease. Measurements were made at 20, 0, 4, 8, and 12 hours.

The Halberg Chronobiology Center consulted with them on how to represent the time for each data point. Time can be represented in a number of formats to accommodate data collection formats, including as a date and time format, or as a number of hours from a given reference time.

A research group in the Physiology and Biophysics Department of the Institute of Biomedical Sciences at the University of São Paulo, Brazil, has been using Mini Mitter behavioral and temperature time series (sampled every 30 seconds during 30 or more days) as well as several variables collected in groups of animals killed every 3 hours along the 24-hour scale to estimate circadian changes. These researchers were looking for time series or biological rhythms analysis software for Macs, specifically for cosinor analysis. We assisted them in the installation and setup of R, Rstudio and CATkit. As a platform-independent tool, CATkit is easily used on Macs as well as PCs.

In Kırşehir, Turkey, at Ahi Evran University, Department of Biology, the circadian time structure of body temperature in the Anatolian ground squirrel is being studied. Body temperature from 28 ground squirrels was recorded intraperitoneally before, during and after hibernation. In order to determine how temperatures change with approaching hibernation, we helped our colleague with detrending, defining inflection points, demonstrating how to perform least squares spectral analysis, and single- as well as multiple-component cosinor analyses with CATkit.

A doctoral student at the Department of Obstetrics and Gynecology at the Haukeland University Hospital in University of Bergen, Norway is analyzing the circadian rhythm of fetal heart rate. With her mentor, she collected fetal heart rate every two seconds for up to 20 hours continuously. Mean fetal heart rate per minute was used to reduce noise.

Our lab helped with assessment of data quality needed for cosinor, and the impact of various sampling/binning intervals for the data (from 2 sec to 10 min). Population-mean cosinor was applied. We discussed the necessity of keeping the actual times associated with the data when recording crosses midnight, and worked with these colleagues on criteria for including/excluding too-short records while retaining as much of the data as possible.

Future Enhancements

CATkit was developed according to formulae and practices refined by the Halberg Chronobiology Center in Minnesota. There are many papers on the methods and theory for cosinor which have been recently reviewed (Cornelissen, 2014).

We are planning to add parameter tests of the cosinor results. These are used to compare rhythm parameters (MESOR, amplitude and acrophase) between two or more individuals, i.e., testing equality of parameters considered singly or jointly.

The Population-Mean Cosinor (PMC) is another method that is important when inferences need to be made for a population. Parameter estimates are based on the means of estimates obtained from individuals representing a random sample of the population, where confidence regions for the true parameters depend on the variability among individual parameter estimates. PMC will be added to CATkit as well.

Parameter tests of PMC results will also be added to CATkit. These are used to compare rhythm parameters (MESOR, amplitude and acrophase) between two or more populations, testing the equality of parameters considered singly or jointly.

R is a commonly used statistical, array-based programming language. Source code can be customized directly. CATkit is found on CRAN (R Core Team, 2017) at https://cran.r-project.org/package=CATkit .

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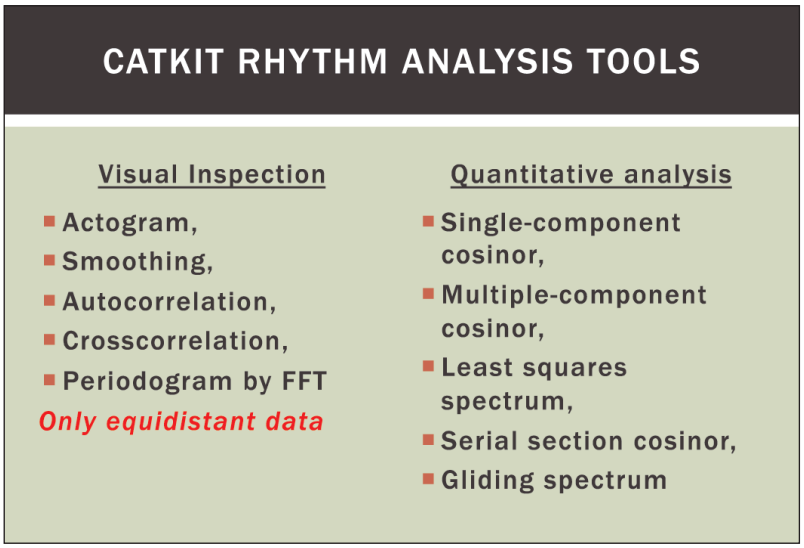

Figure 1: *CATkit includes a number of visualization tools, as well as toolsfor quantitative analyses*

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Lessons Learned from Longitudinal Blood Pressure Monitoring

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Dedicated to the memory of Franz Halberg.

Abstract

A 12-year record of blood pressure measured automatically around-the-clock at 30-minute intervals, with interruptions, by a 74-year old man treated for high blood pressure is analyzed to assess blood pressure variability on a daily basis. The relative merits of a classification in terms of "dipping" based on the day-night ratio are compared with those of a chronobiologic approach based on cosinor rhythmometry to detect vascular variability disorders. Circadian rhythm characteristics show greater stability than the day-night ratio. The circadian amplitude of this patient is found to be modulated by a circannual variation that accounts for an about 10 mmHg larger blood pressure variation in the winter than in the summer. Consequently CHAT (Circadian Hyper-Amplitude-Tension, a circadian amplitude of blood pressure exceeding the upper 95% prediction limit in clinically healthy peers matched by gender and age) is only diagnosed during winter months. This result may underlie the larger incidence of adverse cardiovascular events in the winter than in the summer observed at mid-latitude geographic locations.

Keywords

Blood Pressure, Cardiovascular Disease Risk, CHAT (Circadian-Hyper-Amplitude-Tension), Circadian, Circannual, Day-Night Ratio, Dipping, Temperature, Vascular Variability Disorders.

Introduction

Many studies of blood pressure and blood pressure variability are performed based on clinic measurements, some repeated during consecutive visits [1]. There has also been much interest in ambulatory blood pressure monitoring (ABPM), which has correlated to cardiovascular disease risk better than clinic measurements [1, 2]. These studies, however, are often limited to 24 or at best 48 hours. Longitudinal monitoring has been practiced by means of home measurements [1, 3], often limited to morning and/or evening readings, which are insufficient to assess the circadian variation.

In addition to an elevated blood pressure, blood pressure variability has also been associated with cardiovascular disease risk [4]. A measure of blood pressure variability often used is the day-night ratio, used for a classification in terms of "dipping" [5], even though alterations in the 24-hour rhythm

characteristics of blood pressure have been shown to have a higher predictive value in several outcome studies [6, 7].

The relative merits of assessing alterations in the circadian variability of blood pressure and heart rate in terms of Vascular Variability Disorders [8, 9] or the "dipping" status in terms of the day-night ratio are assessed herein based on a longitudinal record spanning 12 years from a patient treated for high blood pressure.

Subject and Methods

The patient (MM) is a 74-year old hypertensive man at the start of longitudinal monitoring on 15 April 2003. The diagnosis of MESOR-hypertension prompted the initiation of treatment with the calcium antagonist benidipine hydrochloride (4 mg/day) on 22 April 2003. Several adjustments to his treatment were needed to bring his blood pressure within acceptable limits. The dose of benidipine hydrochloride was increased to 8 mg/day on 11 June 2003, then to 12 mg/day on 5 August 2003, and to 16 mg/day on 5 October 2003. On 3 February 2004, the angiotensin II receptor antagonist telmisartan (20 mg/day) was added, and on 4 March 2004, the dose of telmisartan was increased to 40 mg/day. Thereafter, the patient remained on this anti-hypertensive regimen until his death in January 2015.

From 15 April 2003 to 7 January 2015, MM measured his systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) at 30-minute intervals around the clock by ABPM (A&D, Tokyo, Japan), with occasional interruptions. Mean arterial pressure (MAP=SBP/3+2DBP/3), pulse pressure (PP=SBP-DBP), and the pulse pressure product (PPP=SBPxHR/100) were computed. Oscillometric measurements were used for analysis. Unfortunately, data covering about 1 year (in 2007) were lost. Figure 1 displays the entire record of SBP.

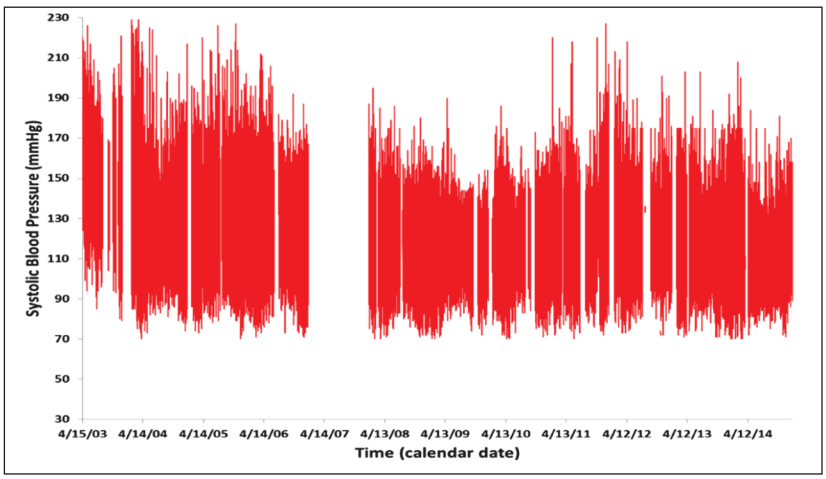

Figure 1: *Complete 12-year record of systolic blood pressure of patient MM (M, 74 years at start).*
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The data were analyzed by sphygmochron [10], overall, by year, and for consecutive days. Parametrically, a 2-component model consisting of cosine curves with periods of 24 and 12 hours was fitted to the data to yield estimates of the MESOR (M, a rhythm-adjusted mean), the 24-hour and 12-hour amplitudes (A) and acrophases (ϕ) (measures of half the extent of predictable change within a cycle, respectively). Non-parametrically, the percentage time elevation, extent and timing of excess above time-specified reference values qualified by gender and age, were computed. The day-night ratio (DNR) was also computed as DNR = (daytime mean – nighttime mean)/24-hour mean, where daytime

is the span from 10:00 to 20:00 and nighttime is the span from 00:00 to 06:00. The DNR is used for classification in terms of 'dipping": Reverse Dipping (RD) when DNR < 0; Non-Dipping (ND) when 0 < DNR < 10%; Dipping (DP) when 10% < DNR < 20%; and Extreme Dipping when DNR > 20%.

Circadian rhythm characteristics (M, A, ϕ) at a trial period of 24 hours were also estimated based on hourly estimates of the original data. Diagnoses based on these estimates considered herein include: MESOR-Hypertension (MH) when the SBP-M and/or DBP-M exceed(s) the upper 95% prediction limit of clinically healthy peers matched by gender and age; Excessive Pulse Pressure (EPP) when PP > 60 mmHg; CHAT (brief for Circadian Hyper-Amplitude-Tension) when SBP-A and/or DBP-A exceeds the upper 95% prediction limit of clinically healthy peers matched by gender and age; ecphasia (ecϕ) when SBP-ϕ and/or DBP-ϕ, but not HR-ϕ lie(s) outside the respective 90% prediction intervals of clinically healthy peers matched by gender and age; and Decreased Heart Rate Variability (DHRV) when the standard deviation (SD) of HR is below 7.5 beats/min.

In view of occasional interruptions of monitoring, criteria needed to be defined to decide whether data were sufficient to obtain reliable estimates of all parameters of the daily analyses. Estimates of M, A, ϕ were deemed acceptable when they were computed based on at least 16 hourly average values. Estimates of the DNR were viewed as acceptable when they were computed on at least 20 original data that included at least 3 nightly and at least 4 daytime measurements. Over the 12-year record, there were 1,969 (44.9%) days with sufficient data to yield acceptable estimates of both DNR and (M, A, ϕ) for a comparison of the occurrence of abnormal patterns of BP and/or HR.

Results

Overall, dipping occurred only 35.6% (SBP) or 30.1% (DBP) of the time. Abnormal DNR values were thus present most of time. They differed, however, from one day to another, with non-dipping found 21.5% (SBP) or 14.1% (DBP) of the time, reverse dipping 4.2% (SBP) or 2.7% (DBP) of the time, and extreme dipping 38.7% (SBP) or 53.0% (DBP) of the time. Daily estimates of the DNR varied between -7.7 and 41.7 for SBP and between -8.4 and 44.6 for DBP, averaging (mean ±SD) 17.4 ± 8.8 in the case of SBP and 20.9 ± 10.1 in the case of DBP. These values cover all 4 categories of "dipping".

Even based on data collected over consecutive years, the diagnosis in terms of "dipping" changed from one year to another. In the case of SBP, the DNR varied from 7.6 (ND) in 2003 to 20.8 (ED) in 2006. Excluding 2003 when treatment was being adjusted, the DNR varied from 12.6 in 2013 to 20.8, averaging (mean ± SD) 17.6 ± 2.8. Likewise in the case of DBP, the DNR varied from 11.7/16.9 (including/excluding 2003) to 25.8, averaging 21.5 ± 3.1.

As seen in Figure 2 for the case of SBP, the large variability in the DNR is not completely random. It follows an about yearly variation. It tends to be higher during the winter and lower during the summer. Similar results are also observed in the case of DBP.

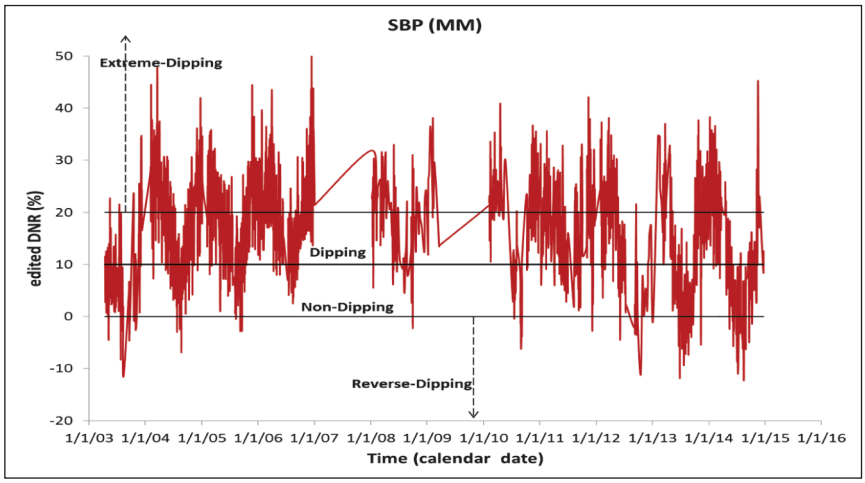

Figure 2: *Daily estimates of the day-night ratio (DNR) vary greatly. DP occurs less than one third of the time. While RD only occurs less than 5% of the time, ED occurs about twice as often as ND. The DNR tends to be larger in winter and smaller in summer. © Halberg Chronobiology Center*

As seen from Figure 3, once treatment has been adjusted, the MESOR of SBP remains within acceptable limits most of the time. Only towards the end of the record does SBP-M decrease below the lower 5% prediction limit of clinically healthy peers matched by gender and age. This trend is in agreement with the time course of SBP-M as a function of age found in healthy populations [11]. Treatment was successful in keeping PP within the acceptable range most (91.1%) of the time, but at the cost of lowering DBP-M below the lower 95% prediction limit during a non-negligible number of days (22.8% of the time), mostly during the second half of the 12-year record.

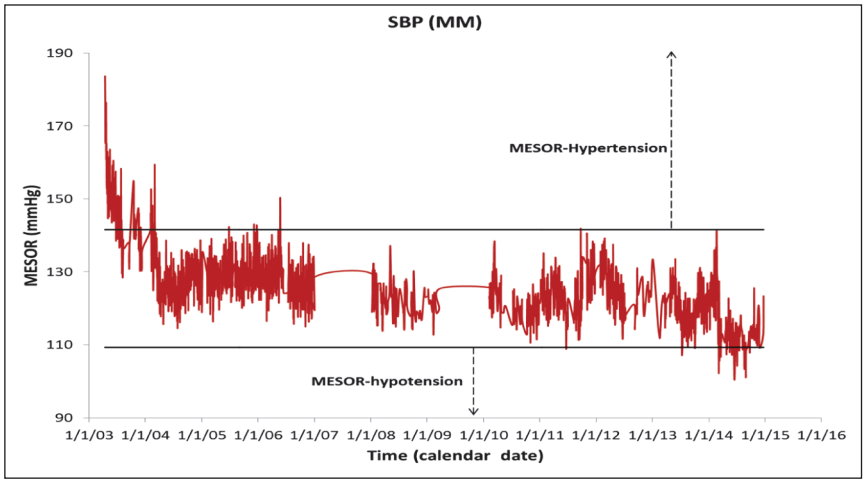

Figure 3: *Daily estimates of SBP-M are within acceptable limits most of the time once anti-hypertensive treatment has been adjusted. © Halberg Chronobiology Center*

Treatment may have contributed to lowering HR below the lower prediction limit in health, and HR-SD below 7.5 beats/min 63.6% of the time. Whereas SBP-A and DBP-A are within acceptable limits most of the time, SBP-CHAT and DBP-CHAT are present 31.9% and 16.2% of the time, respectively. By comparison, ED was 38.7% (SBP) and 53.0% (DBP). The horizontal black line in Figure 4 indicates the upper limit of acceptability for SBP-A for clinically healthy peers matched by gender and age. Above this limit for SBP-A, outcome studies document a marked increase in adverse cardiovascular outcomes.

As seen in Figure 4, SBP-A is modulated by the circannual variation. It is larger in winter and smaller in summer. Similar results are found for DBP. When data are analyzed over consecutive 7-day records, as recommended in a consensus document [8, 9], CHAT is only found in winter.

The presence of VVDs from sphygmochron analyses performed over consecutive years shows more consistency than results presented above for the DNR. MESOR-Hypertension and Excessive Pulse Pressure are only found in 2003 when treatment was initiated and adjusted for dosing. Systolic MESOR-hypotension is only found during the last year of monitoring and may have reflected a natural decline in SBP-M with age [11]. All BP parameters are within acceptable limits, including SBP-A and DBP-A. Only HR-M is consistently below the lower 5% limit of acceptability, varying between 57.3 beats/min during the last year of monitoring in 2014 and 63.6 beats/min in 2004. It may have resulted from the anti-hypertensive treatment since in 2003 HR-M was 66.6 beats/min, within acceptable limits. Likewise, HR-SD tends to be too low, decreasing below 7.5 beats/min from 2008 to 2011.

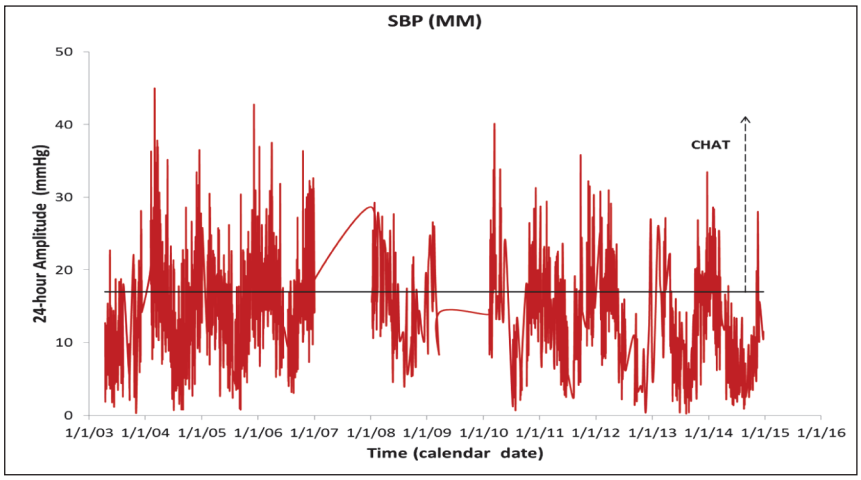

Figure 4: *Daily estimates of SBP-A vary greatly. Modulation by the circannual variation accounts for the fact that CHAT is found 31.9% of the time, but only in winter, SBP-A being larger in winter than in summer.* *© Halberg Chronobiology Center*

Discussion and Conclusion

Least squares spectral analysis of SBP-A as it varied over 12 years detects a peak at a frequency of one cycle per year. Its amplitude is estimated to be about 5 mmHg. This means that SBP-A can be expected to differ by about 10 mmHg between summer and winter. It is a much larger circannual variation than what can be observed for the MESOR of blood pressure. A circannual variation in the circadian rhythm characteristics of blood pressure was already noted earlier in another longitudinal record of a clinically healthy man [12]. Depending on the clock hour of daily measurements, blood pressure peaks in different seasons. The fact that measurements taken around midnight peak in the fall whereas morning measurements peak in the summer and afternoon measurements peak in the winter was interpreted as a circannual modulation of the circadian amplitude of blood pressure [12], Figure 5.

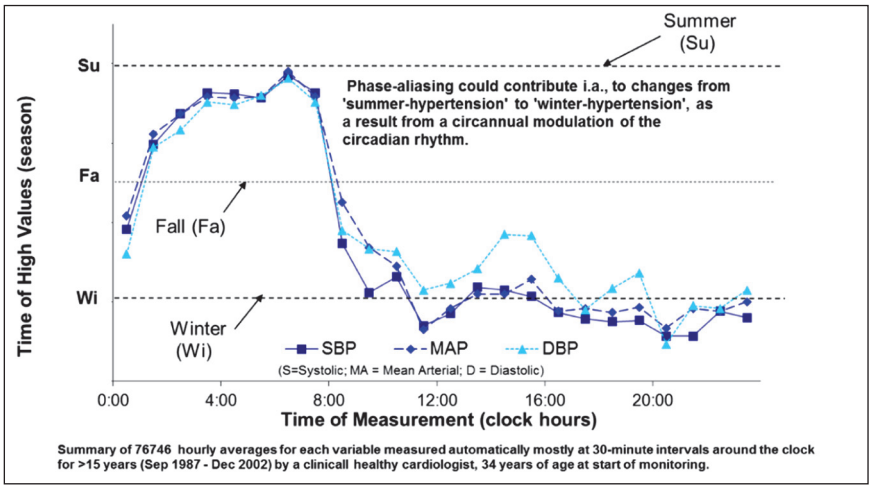

Figure 5: *The change in circannual peak in blood pressure measurements depending on the clock hour when they were taken can be accounted for by a circannual modulation of the circadian amplitude of blood pressure.*
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Environmental cues have been reported to account for a larger proportion of the variability in the day-to-night ratio as compared to genetics [13]. Season and temperature accounted for about 8% of the variance in night-to-day ratio, whereas genetics accounted for less than 1% [13]. A similar conclusion was reached in another study: variation in the day-night difference in blood pressure was reportedly largely non-genetic [14]. Age, total cholesterol, plasma triglycerides, and current smoking were found to be associated with the day-night difference in SBP, whereas age, plasma triglycerides, and current smoking were reportedly associated with the day-night difference in DBP [14]. The direct association between meteorological factors and circadian blood pressure variability has also been examined in 158 subjects who provided 7-day/24-hour ambulatory records [15]. The magnitude of the nocturnal decrease in blood pressure was larger by about 2 mmHg on average on the coldest day than on the warmest day [15]. The incidence of adverse cardiovascular events is also larger in winter at mid-latitude geographic locations [16]. An increase in blood pressure variability during spans of cold weather may complicate the diagnosis and management of hypertension and may contribute to the high cardiovascular mortality observed in winter [17].

In summary, day-to-day variability in circadian rhythm characteristics may account in part for the larger-than-expected incidence of abnormalities detected based on 24-hour records. Results support our recommendation of around-the-clock monitoring for at least 7 days at the outset [8, 9]. Both systolic and diastolic CHAT are detected mostly during winter months.

Systolic MESOR-Hypertension was present at the beginning of the record and was corrected by medication. While the DNR undergoes a yearly variation, RD, ND, DP, and ED occur throughout the year. The limited reproducibility of a classification in terms of “dipping” has been noted earlier [18]. CHAT is present only between October and May, mostly during the winter months. Reference limits may need to account for the circannual variation. The higher incidence of CHAT in the winter, however, is in keeping with the then-higher likelihood of adverse cardiovascular events observed on a population basis [19, 20].

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Spaceflight and Geriatrics

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Abstract

Physiological deconditioning similar to that seen in spaceflight also occurs on Earth, especially as a consequence of the aging process and also due to bedconfinement and/ or immobilization. Illness or injury in older persons frequently requires hospitalized based care. However, the immobilization that occurs during hospitalisation is itself a major factor in physiological deconditioning and functional decline and in older persons can further contribute to a downward spiral of increasing frailty, dizziness upon standing up (orthostatic intolerance) and increased risk and incidence of falls.

Bedrest is used as a ground-based analog for studying the effects of weightlessness on physiological systems as seen during space flight. As older persons spend up to 80% of their time in hospital bed-confined, bedrest studies can also help in furthering our understanding of the deconditioning process during hospitalization in older persons.

Astronauts in space spend substantial time doing physical training to counteract the deconditioning due to the effects of microgravity and to alleviate orthostatic intolerance on return to Earth. Could such physical activity programs carried out by astronauts in space be used during bedrest immobilization in older persons to counteract deconditioning as well?

Recent data generated from bedrest studies related to space research suggest that resistance exercise, together with proper nutrition, is effective in maintaining physiological functionality in astronauts during spaceflights of up to six months duration. Similarly, some studies have suggested that nutritional therapy (e.g high protein diet), along with resistance training, improves lean muscle mass and muscle strength in older persons.

This presentation discusses how knowledge obtained from space research can provide guidance towards optimising health care strategies to tackle bed-confined deconditioning, especially in older persons (”Spaceflight meets Geriatrics!”).

Assoz. Prof. Priv.-Doz. Dr. med. Nandu Goswami, MMedSci PhD.

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